PALLADIUM-CATALYZED FUNCTIONALIZATION OF ALKENES TO PROVIDE BIOLOGICALLY RELEVANT SCAFFOLDS

by

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STATEMENT OF DISSERTATION APPROVAL

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ABSTRACT

ortho-Quinone methides (*o*-QMs) are highly reactive intermediates with various applications in chemical and biological sciences. In the last decade, chemists have utilized *o*-QM reactivity to develop numerous synthetic transformations that provide access to biologically relevant scaffolds, such as chromanes. However, enantioselective functionalization of *o*-QM is still a challenge. Presented herein are functionalization reactions of *o*-QMs with a chiral Pd-catalyst to provide biologically relevant chromane and bis-arylmethane scaffolds in excellent enantioselectivity. These studies are followed by development of hydrofunctionalization of vinyl phenols and vinyl indoles to provide the corresponding bis-arylmethanes.

In the first study, a unique approach to alkene difunctionalization was taken based on a mechanistic hypothesis of a quinone methide intermediate in a related reaction. Substrates containing an alkene adjacent to an *ortho*-phenol and a tethered nucleophile were prepared, allowing for the regioselective addition of two distinct nucleophiles. The reaction was applied to the dialkoxylation of alkenes, resulting in the enantioselective formation of heterocyclic compounds bearing two adjacent chiral centers.

In the second study, a Pd-catalyzed enantioselective reaction of indoles with *o*-QMs was developed, using a similar strategy as above, to provide bis-arylmethanes. Since many biologically active compounds contain bis-arylmethane functionality, several of the newly synthesized compounds were screened against breast cancer cell lines. Two

of newly synthesized bis-arylmethanes, **69** and **72**, demonstrated micromolar anti-cancer activity against breast cancer cell lines with different phenotypes.

Inspired by promising biological activity of bis-arylmethanes, a unique hydrofunctionalization reaction of vinyl phenol with heteroaromatics was developed to provide analogous structures. The key development in this process is use of alkyl chloride as a sacrificial hydride source to provide the requisite Pd-hydride.

Finally, acid-catalyzed hydrofunctionalization of vinyl indoles with heteroaromatics was developed. This process provides unsymmetrical bis-indolylmethanes in high yields. The biological studies of newly synthesized compounds demonstrated anti-cancer activity against breast cancer cell lines. One of the newly synthesized compound, **149**, demonstrated excellent deferential activity between wild-type breast cell lines and cancerous cell lines.

Dedicated to my parents

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LIST OF ABBREVIATIONS

3 Å MS	three angstrom molecular sieves
Ac	acetyl
AcCl	acetyl chloride
Ac_2O	acetic anhydride
AcOH	acetic acid
*t*AmylOH	*tert*-Amyl alcohol
aq.	aqueous
atm	atmosphere
BBN	9-Borabicyclo (3.3.1) noname
BHT	2,6-di-*tert*-butyl-4-methylphenol
Bn	benzyl
bs	broad singlet
Boc	*tert*-Butyloxycarbonyl
Bu	butyl
*i*Bu	*iso*-butyl
*i*BuOCOCl	*iso*-butyl chloroformate
*t*Bu	*tert*-butyl
°C	degrees Celsius
ca.	circa

calcd	calculated
Cbz	carbobenzyloxy
CH_2Cl_2	dichloromethane
$CHCl_3$	chloroform
cm	centimeter
cod	cyclooctadiene
d	doublet
Δ	heat
DAST	diethylaminosulfurtrifluoride
DCC	*N,N′*-dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
EC_{50}	effective concentration at 50%
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	enantiomeric excess
equiv.	equivalents
er	enantiomeric ratio

ESI	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
FTIR	fourier transform infrared spectroscopy
g	gram
GC	gas chromatography
h	hour
hν	ultraviolet light
HOBt	Hydroxybenzotriazole
HPLC	high pressure liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
IC_{50}	inhibitory concentration at 50%
IR	infrared spectroscopy
KO*t*Bu	potassium *tert*-butoxide
L	liter
LFER	linear free energy relationship
LG	leaving group
$LiAlH_4$	lithium aluminum hydride
m	multiplet

M	molar
m	*meta*
MCF	Michigan Cancer Foundation
Me	methyl
MeCN	acetonitrile
MeOCOCl	methyl chloroformate
MeOH	methanol
mg	milligram
MHz	megaHertz
min	minute
mL	milliliter
μL	microliter
mmol	millimole
μmol	micromole
mol	mole
mp	melting point
MS	mass spectrometry
MsOH	methylsulfonic acid
MTS	(3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium)
NMM	*N*-methylmorpholine
NMR	nuclear magnetic resonance
Nu	nucleophile

o	*ortho*
OAc	acetate
obsvd.	observed
OTf	trifluoromethylsulfonate
p	*para*
Ph	phenyl
ppm	parts per million
*i*Pr	*iso*-propyl
*i*PrOH	*iso*-propyl alcohol
pyrox	pyridine oxazoline
q	quartet
quinox	quinoline oxazoline
RDS	rate determining step
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
R_f	retention factor
rt	room temperature
s	singlet or second
SFC	supercritical fluid chromatography
sub	substrate
t	triplet
TBAF	tetrabutylammonium fluoride

TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TSE	2-(trimethylsilyl)ethyl
tol	toluene
Ts	Tosyl
TsCl	*para*-toluenesulfonyl chloride
TsOH	*para*-toluenesulfonic acid
UV	ultraviolet
vs.	versus

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CHAPTER 1

RECENT DEVELOPMENTS IN THE SYNTHESIS AND APPLICATIONS OF *ORTHO*-QUINONE METHIDE INTERMEDIATES

Introduction

Quinone methide (QM) intermediates are ubiquitous in various areas of chemical and biological research.[1-6] There are three possible regioisomers of QM, namely *ortho*-QM (*o*-QM), *meta*-QM (*m*-QM) and *para*-QM (*p*-QM). From these, the *o*-QM and *p*-QM are the most studied and are of broad synthetic interest. The parent *o*-QM, **1**, is a molecule having a cyclohexadiene core with a carbonyl group and a methylene unit attached. It is related to *o*-quinone, **2**, which has two carbonyl groups, and to *o*-quinone dimethide, **3**, which has two methylene units. Unlike intermediates **2** and **3**, which have two identical groups, *o*-quinone methides are highly polarized and, therefore, quite reactive. This reactivity can be rationalized by considering the resonance hybrid of two principal canonical forms **4**, which is aromatic and exhibits charge separation, and **1**, which is nonaromatic (Figure 1.1). From these canonical forms, the reactivity of QM intermediates is understood, wherein nucleophiles reacts at the C-center and electrophiles at the O- center. Generation of the aromatic ring, which results from this reactivity, provides a the life-time of QM intermediates in solution is generally very short and thus in situ formation is necessary.

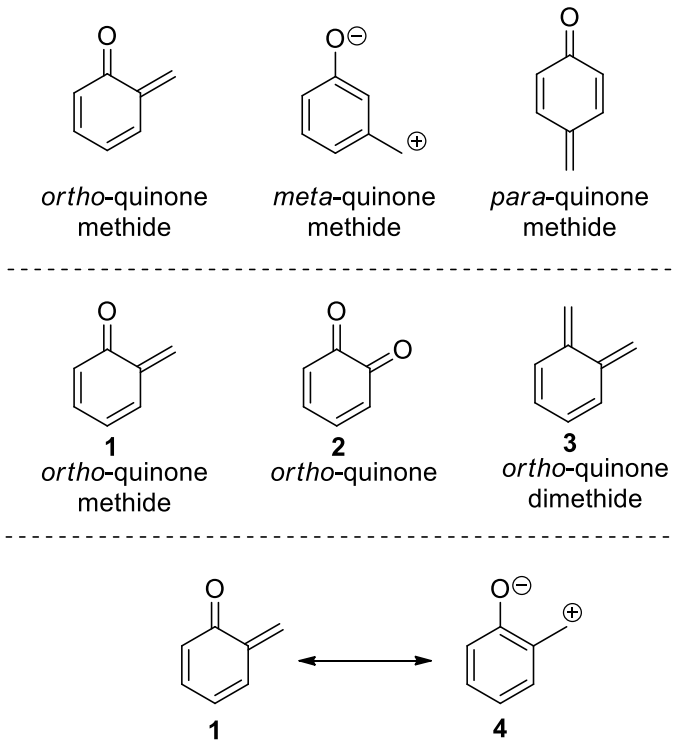

Figure 1.1. Regioisomers and resonance forms of *o*-QM

Quinone methides are useful intermediates with wide applications in organic synthesis,[1-2] materials chemistry,[5] and biology.[5,7] The *o*-QM intermediates are known to undergo 1,4-conjugate addition reactions with nucleophiles and Diels-Alder reactions with various dienophiles (Figure 1.2). Additionally, the biological activity of vitamins E and K, as well as the anti-cancer effects of drugs like anthracyclin antibiotic are purportedly due to *o*-QM formation (Figure 1.3).[8-10] Because of their extensive applicability, various methods are available for their synthesis under thermal, acidic, basic, and neutral conditions.[6] In this chapter, recent developments regarding the generation of *o*-QMs and their applications will be discussed.

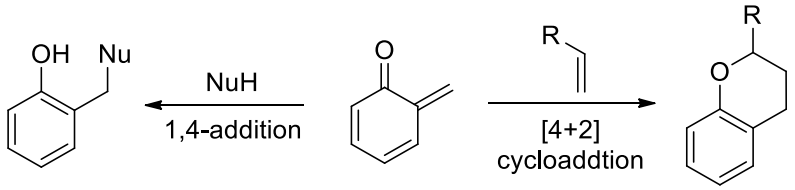

Figure 1.2. General modes of reactivity in *o*-QM

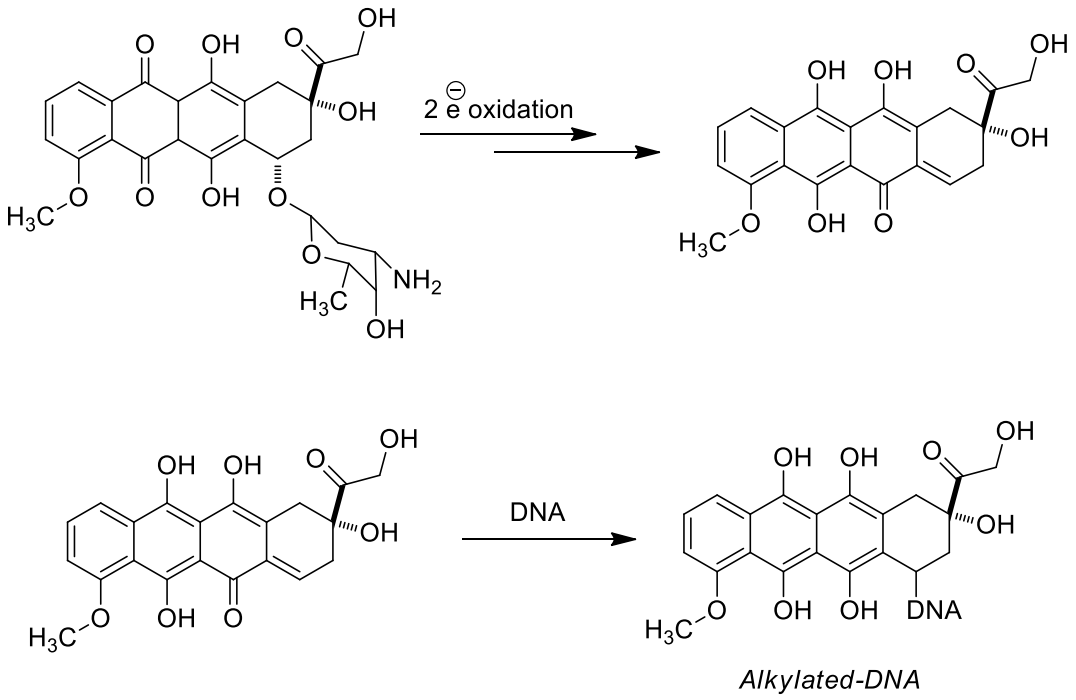

Figure 1.3. Alkylation of DNA by anthracyclin antibiotic: a proposed reason for its biological activity.

Evidence for *o*-QM Existence

In 1907, Fries first suggested the existence of *o*-QM intermediates based on his observations and isolation of dimers and trimers of *o*-QMs.[11] Subsequently, various indirect evidence (such as observed reactivity with enol ethers) supported the existence of *o*-QMs as reactive intermediates in a variety of reactions. In 1963, Gardner and coworkers were the first to analyze the *o*-QM intermediate spectroscopically at -100 °C, which provided solid evidence of their existence.[12-15] Since then a number of *o*-QMs with bulky substituents and/or extended conjugation have been isolated and characterized.

In 1998, Amouri and coworkers reported the first example of a transition metal complex of the simplest *o*-QM (**1**) with Ir. The complex was characterized by X-ray to provide tangible evidence of its existence (vide infra).[1,16-18]

Synthetic Preparation and Utility

The major issue with reactions of *o*-QMs is formation of its dimers and trimers. Nature overcomes this problem by producing highly reactive *o*-QMs in low concentrations and in the vicinity of a reactive site, which makes these undesired reactions less likely. In the laboratory setting such control is difficult to achieve. However, side product formation can be reduced by using a large excess of the subsequent reaction partner. In order to more effectively direct the reactivity of *o*-QM, biologically inspired methods for in situ *o*-QM generation have been reported, including 1) thermolysis, 2) tautomerization, 3) acid catalysis, 4) base catalysis, 5) oxidation and 6) photolysis (Figure 1.4).[6] Some of these methods require forcing conditions, and thus, are not used often. Recently, various groups have reported milder reaction conditions to

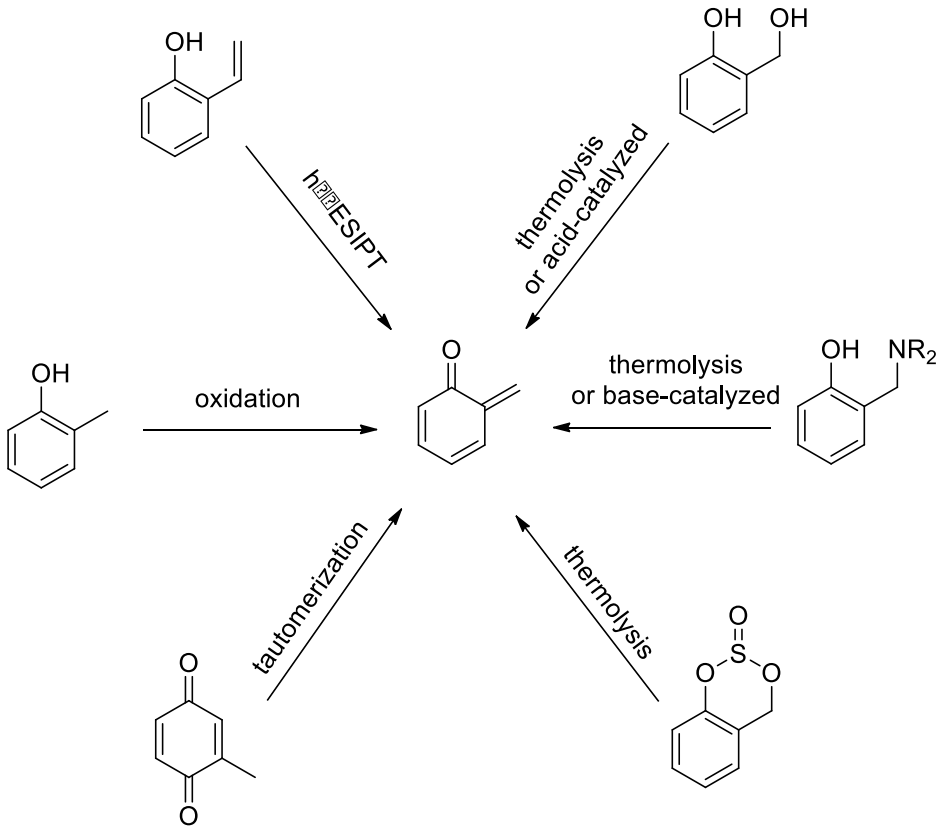

Figure 1.4. Various bio-inspired methods to prepare *o*-QM

form *o*-QMs in situ. Below, some of the key developments in the last decade are discussed in detail.

Metal Free *o*-QM Formation and Utility

In 1995, Mitchell and coworkers reported a reaction of dicarbonate **5** with $NaBH_4$ to give the ketone reduction product monoprotected resorcinol **6** (Figure 1.5).[19] This unique route to monoprotected resorcinol derivatives is proposed to proceed by the mechanism shown in Figure 1.6. The reaction of $NaBH_4$ with **5** leads to the formation of intermediate **A**, which then undergoes carbonate migration to give an intermediate **B**. This decomposes to give *o*-QM **C**, which further reacts with the hydride reagent, followed by protonation to yield the desired product **6**.

Inspired by these results, Pettus and coworkers developed a unique method to generate *o*-QM intermediates under relatively mild conditions, where the reaction of O-Boc protected phenol with organolithium or Grignard reagents leads to the formation of dialkylated phenols in an excellent yield (Figure 1.7).[20-23] This three component reaction allows for the addition of two different Grignard and/or organolithium reagents. The proposed mechanism is similar to that described in Figure 1.6, except the reaction is initiated by addition of RM (organometallic reagents) instead of hydride (Figure 1.8). The reaction of **5** with the first R^1M gives intermediate **A**, which undergoes Boc migration to give intermediate **B**. This decomposes to an *o*-QM with elimination of an equivalent of carbon dioxide, which reacts with R^2M to give the dialkylated phenol as the product.

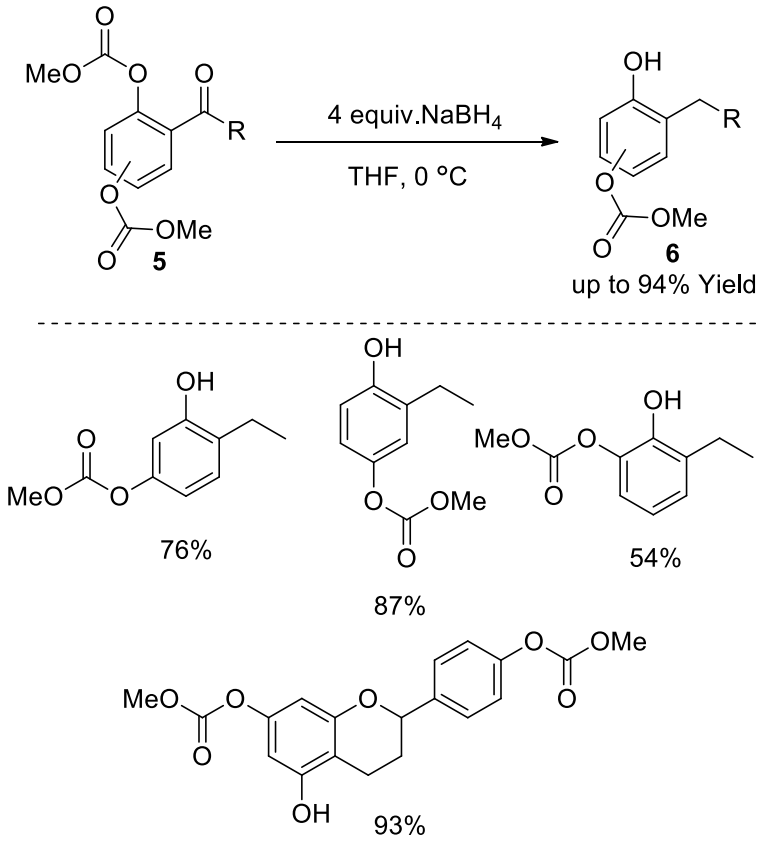

Figure 1.5. Synthesis of monoprotected resorcinols. Data from Mitchell and coworkers.

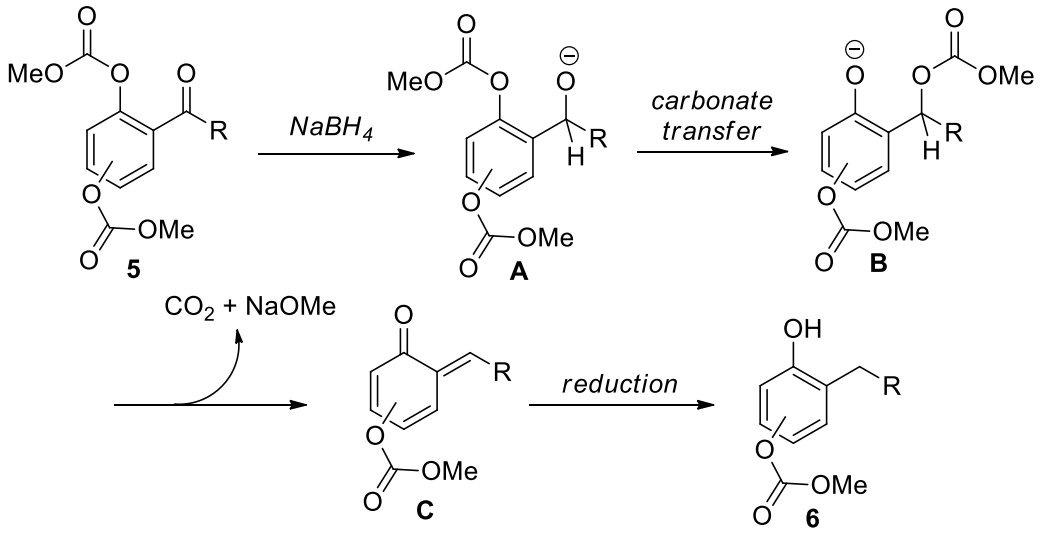

Figure 1.6. Proposed mechanism. Data from Mitchell and coworkers.

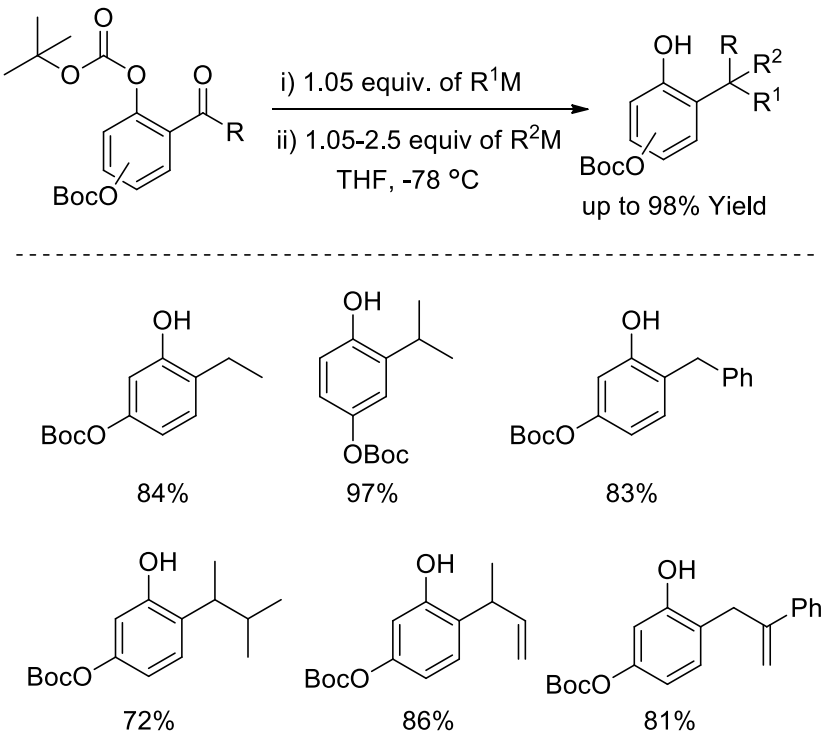

Figure 1.7. Synthesis of *ortho*-alkylated phenols. Data from Pettus and coworkers.

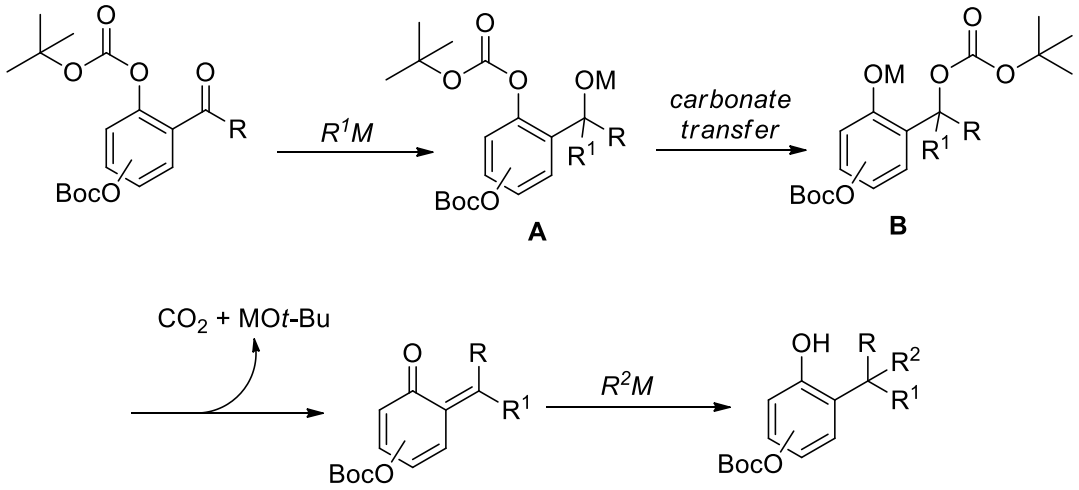

Figure 1.8. Proposed mechanism. Data from Pettus and coworkers.

More recently, Pettus and coworkers extended this method to include enol ethers as the exogeneous nucleophile (Figure 1.9).[24-25] Enol ethers are known to undergo an inverse electron demand [4+2] cycloaddition reaction with *o*-QMs to give chromane frameworks. Chromanes are important substructures found in many natural products and pharmacophores that displays various biological activities such as anti-cancer and anti-HIV effects.[2,26-32] Pettus and coworkers also utilized their base-triggered synthesis of *o*-QMs for the synthesis of various natural products.[33-37] One representative example is shown in Figure 1.10.[37] In this elegant synthesis of berkelic acid via a cycloaddition reaction, an *o*-QM precursor was used to synthesize the core of berkelic acid, which allowed for subsequent functionalization of the chromane core.

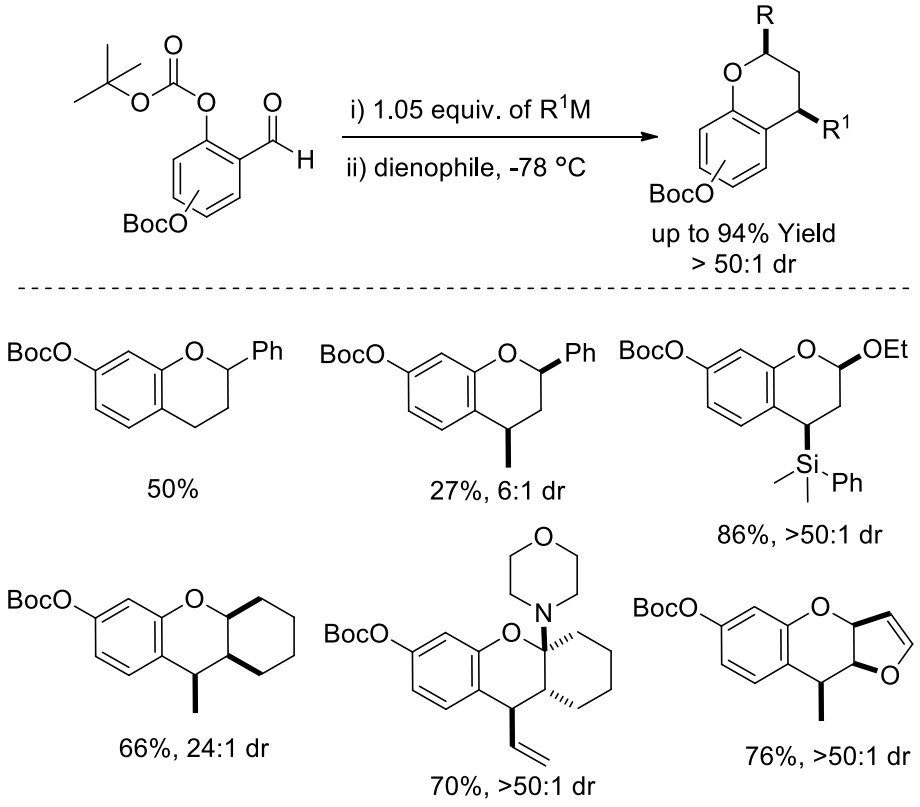

Figure 1.9. Synthesis of chromanes. Data from Pettus and coworkers.

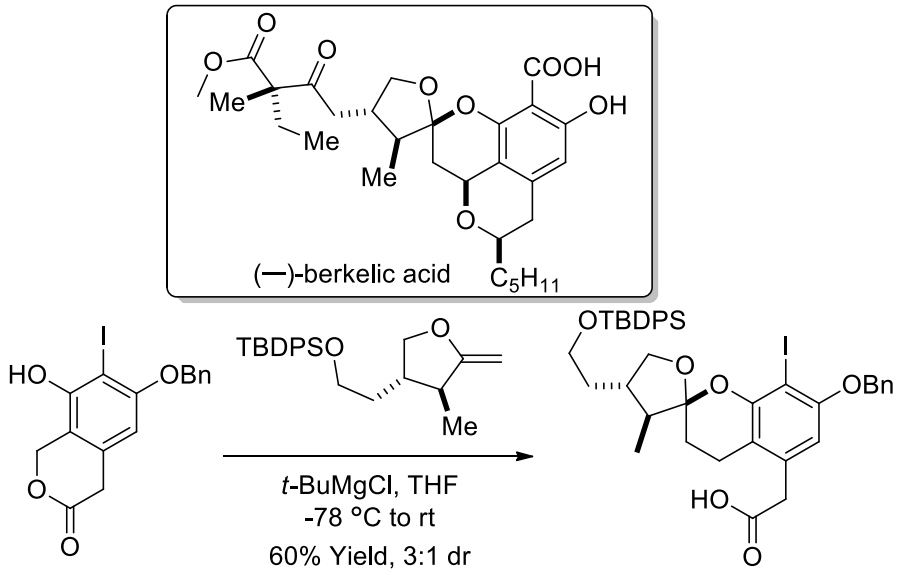

Figure 1.10. Key step towards berkelic acid synthesis. Data from Pettus and coworkers.

In 2003, Ohwada and coworkers reported a unique method to generate 4*H*-1,2-benzoxazines.[38] In this report, they showcased **7** as an excellent precursor for the generation of *o*-QM at relatively lower temperatures (Figure 1.11). Later in 2007, the authors extended this study to incorporate various classes of nucleophiles that react with benzoxazine derived *o*-QM.[39-40] The reaction proceeded smoothly to provide chromanes in good to excellent yield with various dienophiles. Of particular note, highly electron deficient *o*-QMs, which were thought to be unreactive prior to this report, reacted under these conditions. Additionally, in situ generated *o*-QMs reacted with relatively electron poor imines to yield either 3,4-dihydro-1,3-benzoxazines or benzylic amines.

In 1997, Rokita and coworkers reported a novel method to generate *o*-QMs from the corresponding silyl phenol.[41-42] A distinctive use of this method recently came from Scheidt and coworkers for the reaction of *o*-QM with acyl anions to give α-aryl ketones (Figures 1.12 and 1.13).[43] Here, both reaction partners were generated in situ using

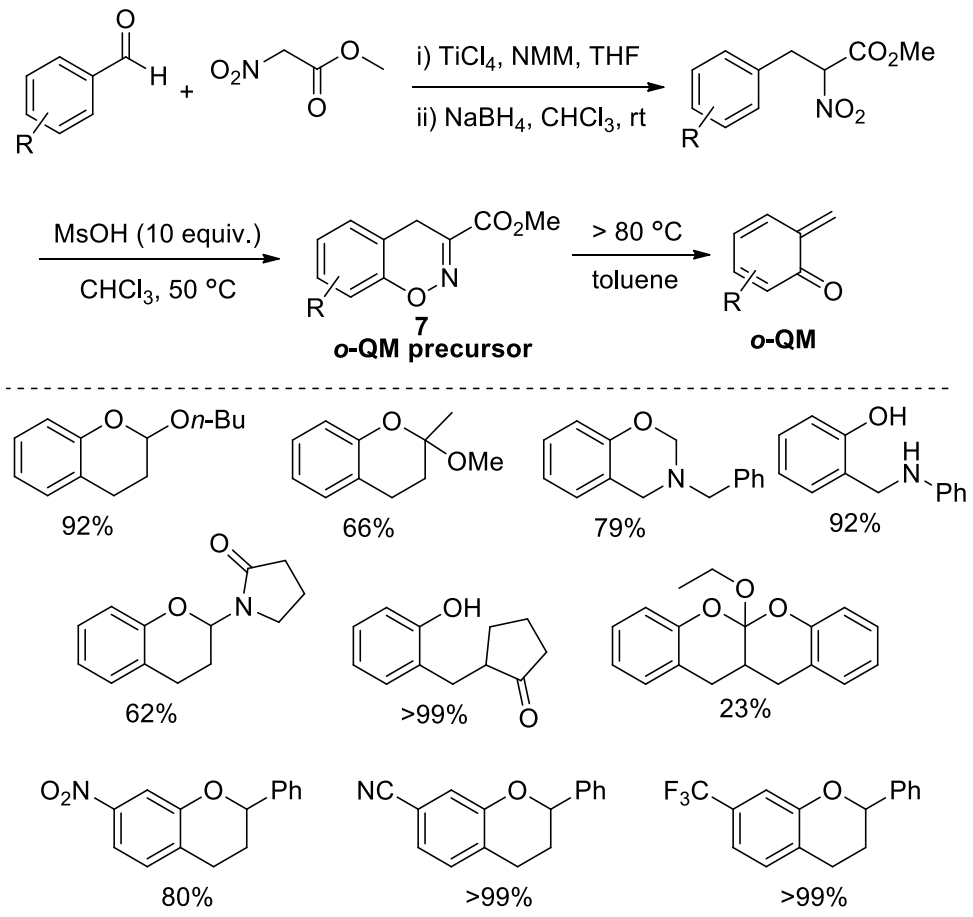

Figure 1.11. *o*-QM from 4*H*-1,2-Benzoxazines. Data from Ohwada and coworkers.

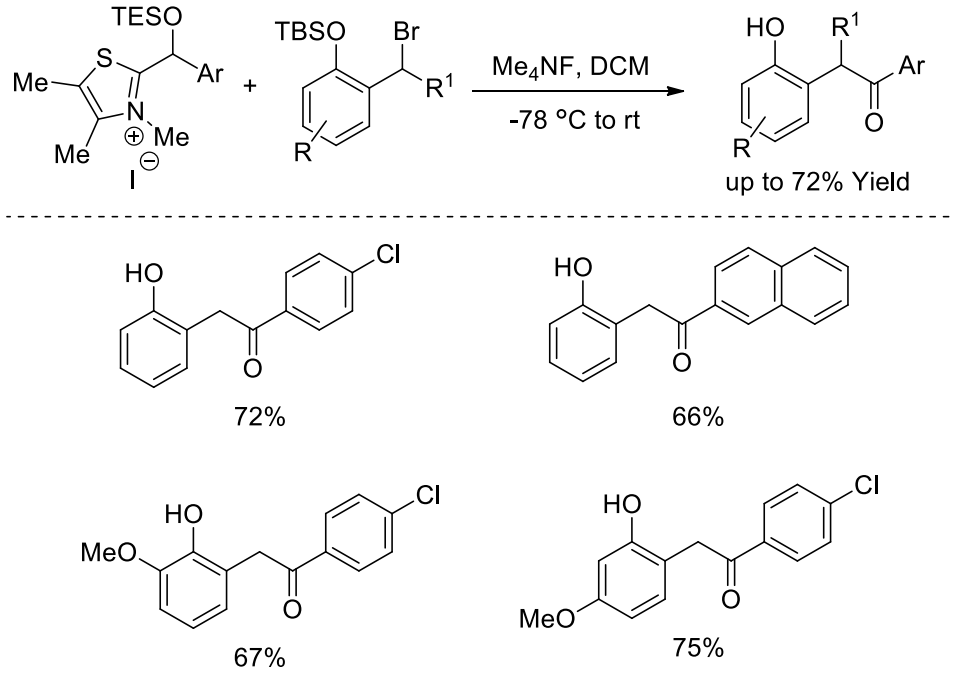

Figure 1.12: Synthesis of aryl ketones. Data from Scheidt and coworkers.

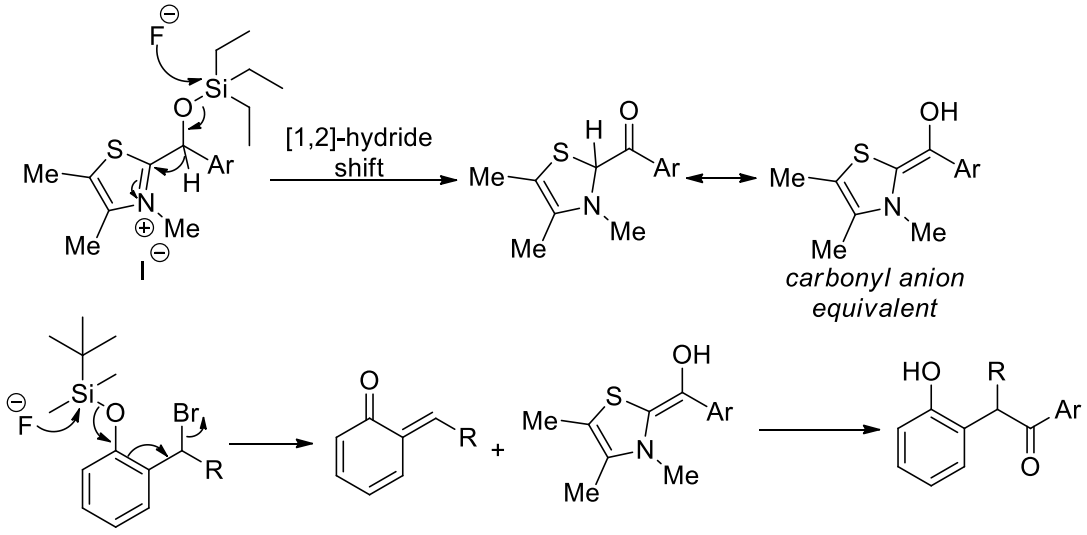

Figure 1.13. Proposed mechanism of in situ generation of both reactive intermediate. Data from Scheidt and coworkers.

fluoride as the common initiator. Hanson and coworkers also utilized a similar approach to generate eight-membered sultams via a formal [4+4] cyclization of *o*-QM (Figure 1.14).[44]

o-QM with Transition Metals

Os- and Ir-Mediated *o*-QM Generation

In 1994, Hermann and coworkers reported the first metal complex of an *o*-QM.[45] The Os-complex was generated via reaction of an Os-complex of *p*-cresol with excess of crotonaldehyde (Figure 1.15). The complex **8** was characterized by NMR spectroscopy

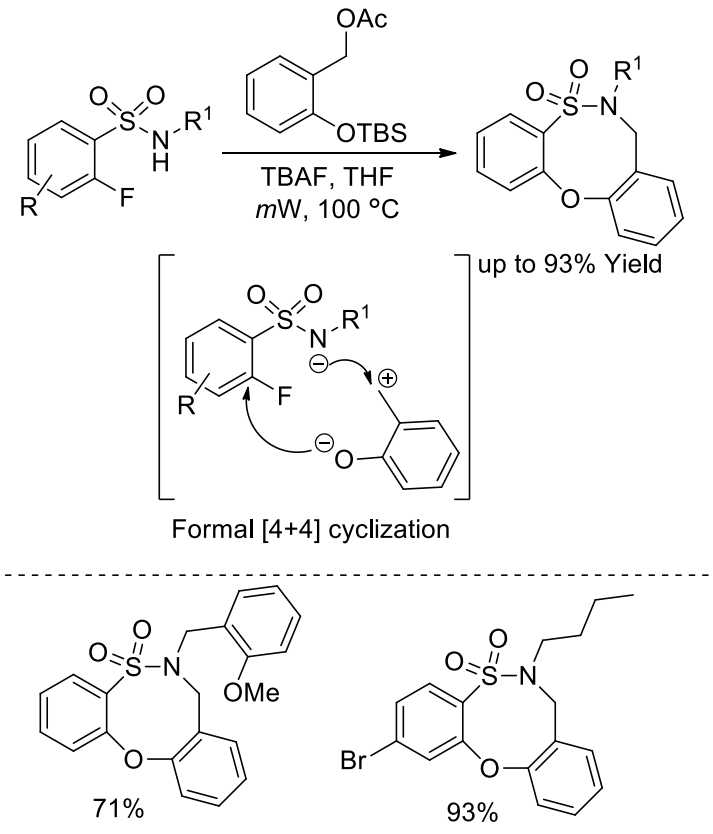

Figure 1.14. Generation of eight-membered sultams via a formal [4+4] cyclization of *o*-QMs. Data from Hanson and coworkers.

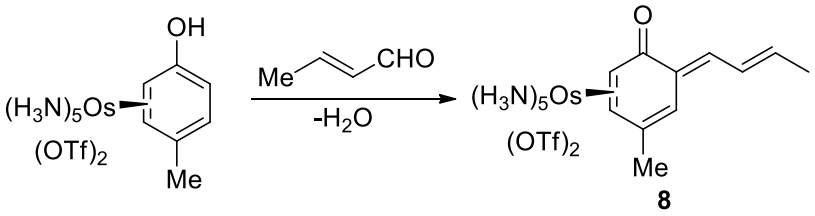

Figure 1.15. Os-complex of *o*-QM. Data from Hermann and coworkers.

Later, in 1998 Amouri and coworkers reported the first example of an Ir-complex of a simple *o*-QM, i.e. an *o*-QM not bearing substituents on the exocyclic double bond.[1,16] Previously, the parent *o*-QM was only observed via NMR spectroscopy at -100 °C. The treatment of the oxo-η^5-dienyl iridium complexes **9** with NaOMe/methanol or *t*-BuOK/CH_2Cl_2 for several hours at room temperature and subsequent reaction workup afforded a yellow microcrystalline η^4-*o*-quinone methide complex **10** (Figure 1.16). This complex was characterized by X-ray to give the first concrete evidence of the existence and structure of an *o*-QM. Interestingly, *o*-QM complex **10** showed *umpulong* reactivity i.e. *o*-QM in complex **10** has nucleophilic character and reacted with electrophiles. For example, when complex **10** was treated with I_2, it gave complex **11** as the major product.

Pd-Catalyzed *o*-QM Generation and Its Reactions

In 1971, Chapman and coworkers were the first to suggest the formation of *o*-QMs from vinyl phenols using stoichiometric $Pd(OAc)_2$ (Figure 1.17).[46] They used this method for the oxidative coupling of a vinyl phenol to form the natural product carpanone via dimerization of *o*-QM. In 2006, Sigman and Schultz reported a unique Pd-catalyzed difunctionalization reaction of vinyl phenols (Figure 1.18).[47] They observed

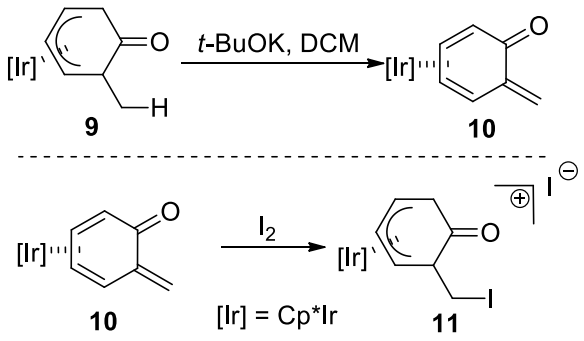

Figure 1.16. Ir-complex of *o*-QM. Data from Amouri and coworkers.

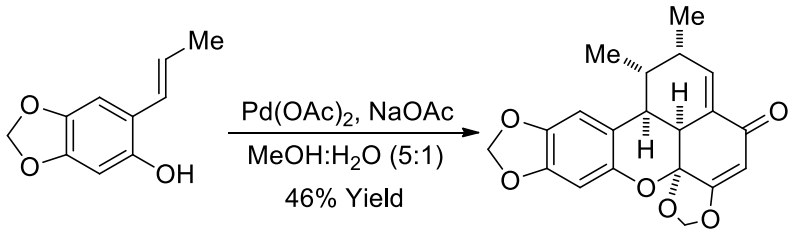

Figure 1.17. Pd-catalyzed total synthesis of carpanone. Data from Chapman and coworkers.

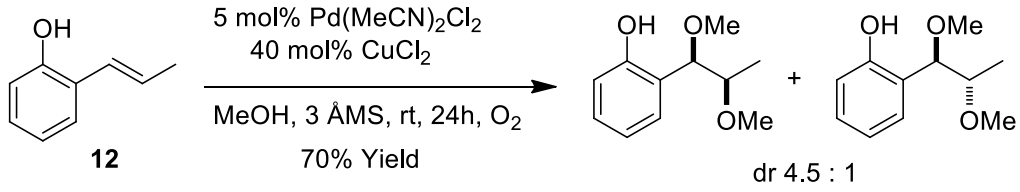

Figure 1.18. Pd-catalyzed dialkoxylation of vinyl phenols. Data from Sigman and coworkers.

addition of two alcohol molecules across the double bond, when vinyl phenol **12** was treated with MeOH and $Pd(MeCN)_2Cl_2$ as the catalyst. The scope of this reaction was limited to the use of simple alcohols. Furthermore, the alcohol was used as the solvent. This reaction was proposed to proceed via a unique mechanism involving an *o*-QM intermediate, where the coordination of the alkene with Pd followed by an intermolecular nucleopalladation resulted in Pd-alkyl intermediate **A** (Figure1.19). The Pd-alkyl **A** decomposes to an *o*-QM with concomitant reduction of Pd. Then, the *o*-QM intermediate **B** reacts with a second equivalent of nucleophilic solvent to give the desired product.

The proposed mechanism was supported by the following experiments: reaction of protected phenol substrate **13** did not yield difunctionalized product instead a mixture of regioisomeric Wacker products were obtained via hydrolysis of the acetals upon workup, supporting the essential role of phenol (Figure 1.20). Second, a deuterium labeling study was performed in which substrate **12** was submitted to the dialkoxylation reaction in CD_3OD. No deuterium incorporation into the alkyl chain of the product was observed. Furthermore, exposure of the isotopically labeled substrate **14** to the reaction conditions resulted in no deuterium transfer within the product (Figure 1.20). These experiments suggest that no β-hydride elimination of substrate or nucleophile occurred during the reaction.

Interestingly, when EtOH rather than MeOH was used as the solvent and (−)-sparteine was used as a ligand, the authors observed the hydroalkoxylation product **15** as the major product (Figure 1.21).[48] Under optimized conditions, various alcohols can be used as both the nucleophile and hydride source.

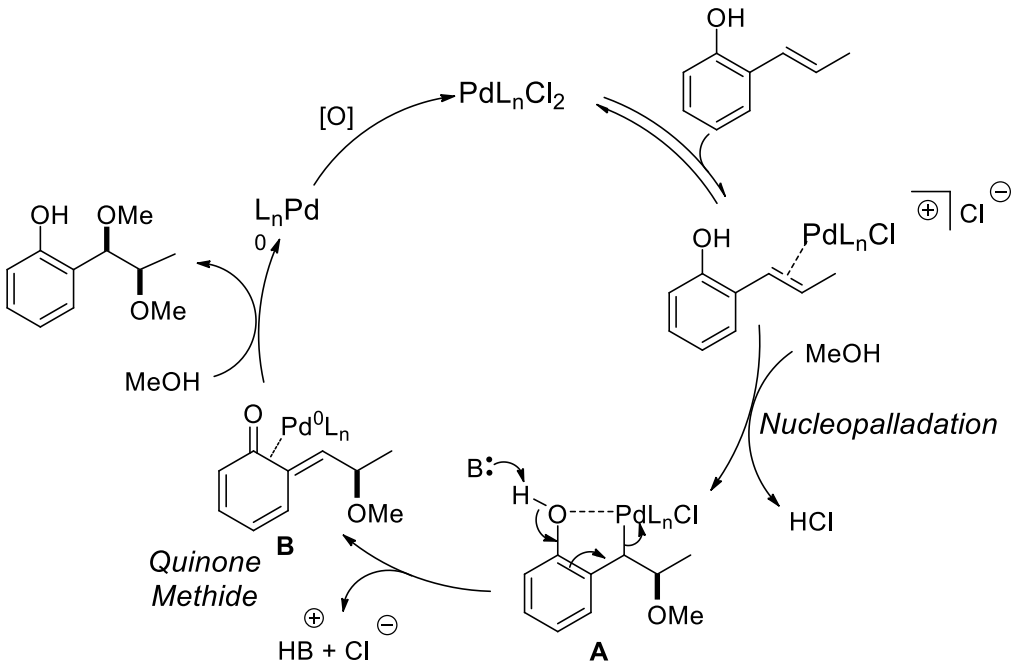

Figure 1.19. Proposed mechanism for Pd-catalyzed dialkoxylation. Data from Sigman and coworkers.

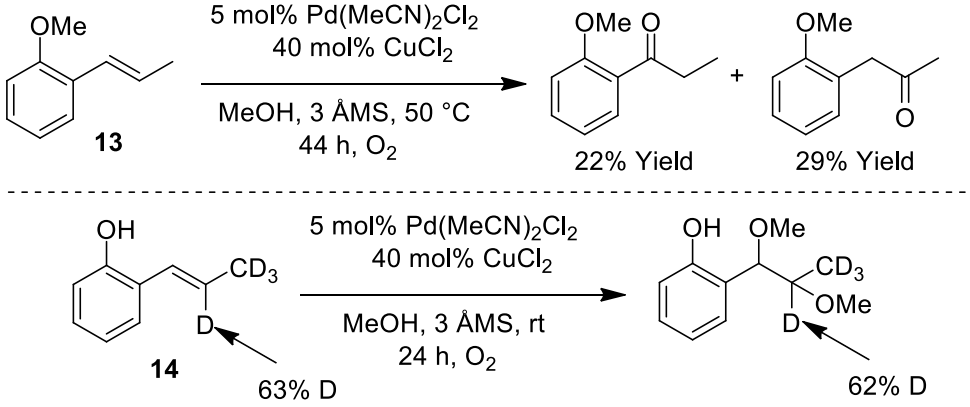

Figure 1.20. Dialkoxylation of protected phenol **13**. Data from Sigman and coworkers.

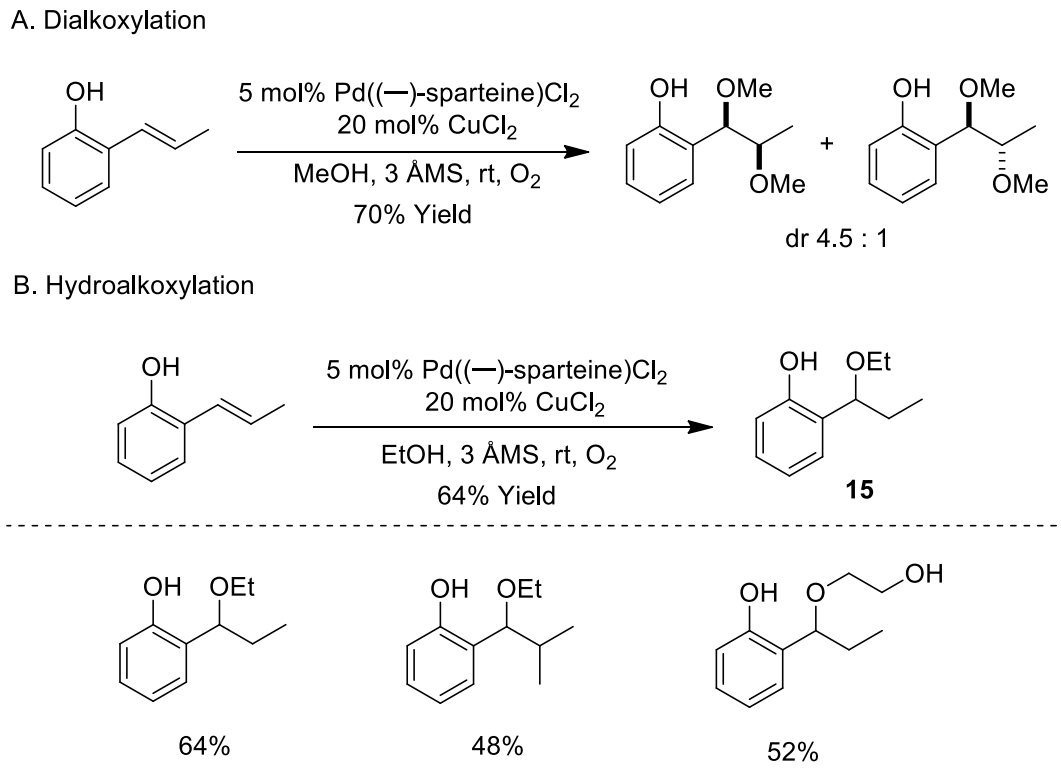

Figure 1.21. Effect of solvent in Pd-catalyzed alkene functionalization of vinyl phenols. Data from Sigman and coworkers.

The major limitation of this reaction is utilization of the nucleophilic alcohol as solvent, which clearly prohibits the use of precious alcohols or alcohols in the solid state. Later, the authors expanded the scope of this transformation to include *sec*-phenyl ethyl alcohol as a sacrificial alcohol, which allowed for the use of other solvents and more precious alcohols as nucleophiles (Figure 1.22).[49]

A Pd-catalyzed alcohol oxidation is proposed to be the source of Pd-hydride **A**, which reacts with alkene to give Pd-alkyl intermediate **B** (Figure 1.23). Pd-alkyl **B** decomposes to give *o*-QM, which reacts with an equivalent of the solvent to give the hydroalkoxylation product. The proposed mechanism was supported by the following

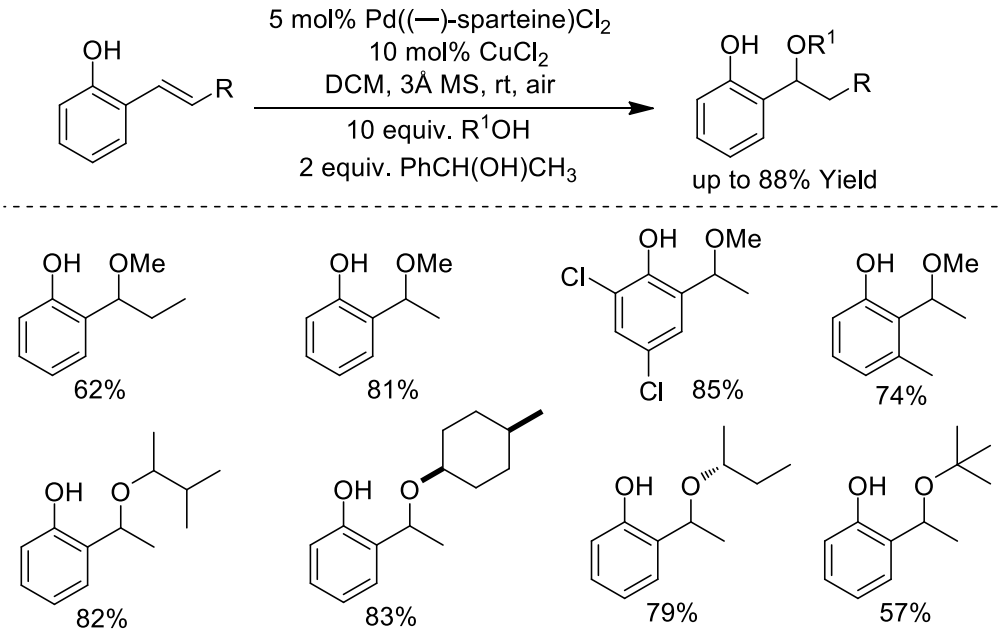

Figure 1.22. Scope of Pd-catalyzed hydrofunctionalization of vinyl phenols using a sacrificial alcohol as the hydride source. Data from Sigman and coworkers.

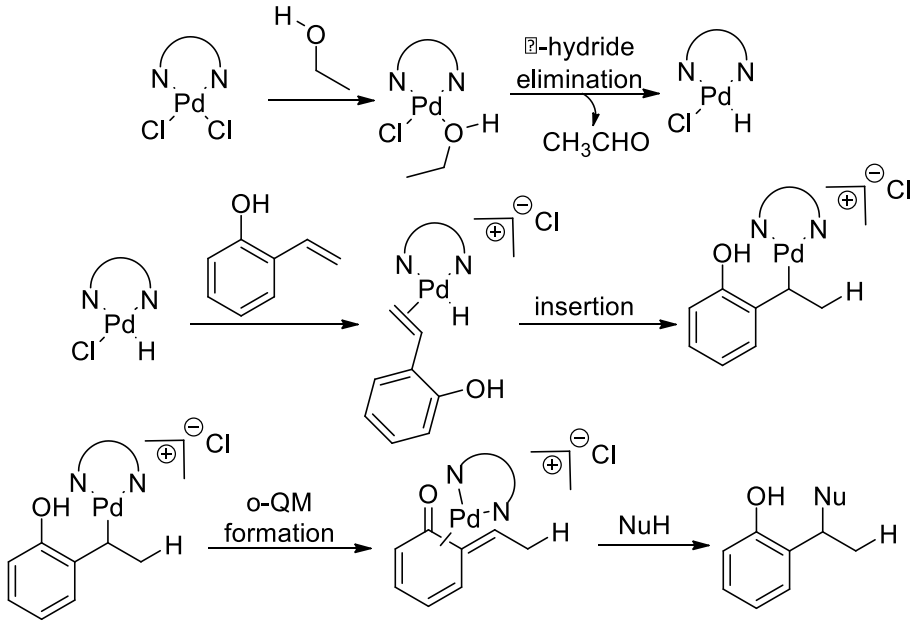

Figure 1.23. Proposed mechanism. Data from Sigman and coworkers.

observations: 1) the use of $PhCD(OH)CH_3$ as the sacrificial alcohol results in two isotopomers **16** and **17** in a 2.5:1 ratio, consistent with the proton incorporated into the product being derived from the oxidation of *sec*-phenethyl alcohol, 2) the reaction of **18** with an enol ether gave chromane **19** in 19% yield, which provides strong evidence for the intermediacy of an *o*-quinone methide under the hydroalkoxylation reaction conditions (Figure 1.24).

Asymmetric Reactions of *o*-QM

Pettus and coworkers were the first to demonstrate substrate-controlled asymmetric reactions of *o*-QMs.[25] Using their three component coupling method with chiral (non-racemic) enol ethers, the desired chromanes were produced with excellent diastereoselectivity (Figure 1.25). The major limitations of this method were 1) availability of chiral enol ethers, and 2) chiral enol ethers were used as a source of chirality hence, only chiral (non racemic) chromanes can be obtained using this method.

In 2009, Lectka and coworkers reported a catalytic, asymmetric cycloaddition of an *o*-QM with a ketene enolate.[50] Chiral cinchona alkaloid-derived tetra-alkyl ammonium fluoride **21** was used as a pre-catalyst to generate the ketene enolate in situ (Figure 1.26). Unfortunately, the scope of the reaction was limited to only **20** as the *o*-QM. The proposed mechanism, shown in Figure 1.27 is initiated by fluoride ion-promoted desilylation of the ketene acetal **22**, forming chiral ion-paired ketene enolate **A**. The resultant ketene enolate regioselectively alkylates the *o*-QM at the methide carbon to give intermediate **B**. Subsequently, **B** undergoes lactonization to form the desired cycloadduct **23**, releasing 2-naphthoxide.

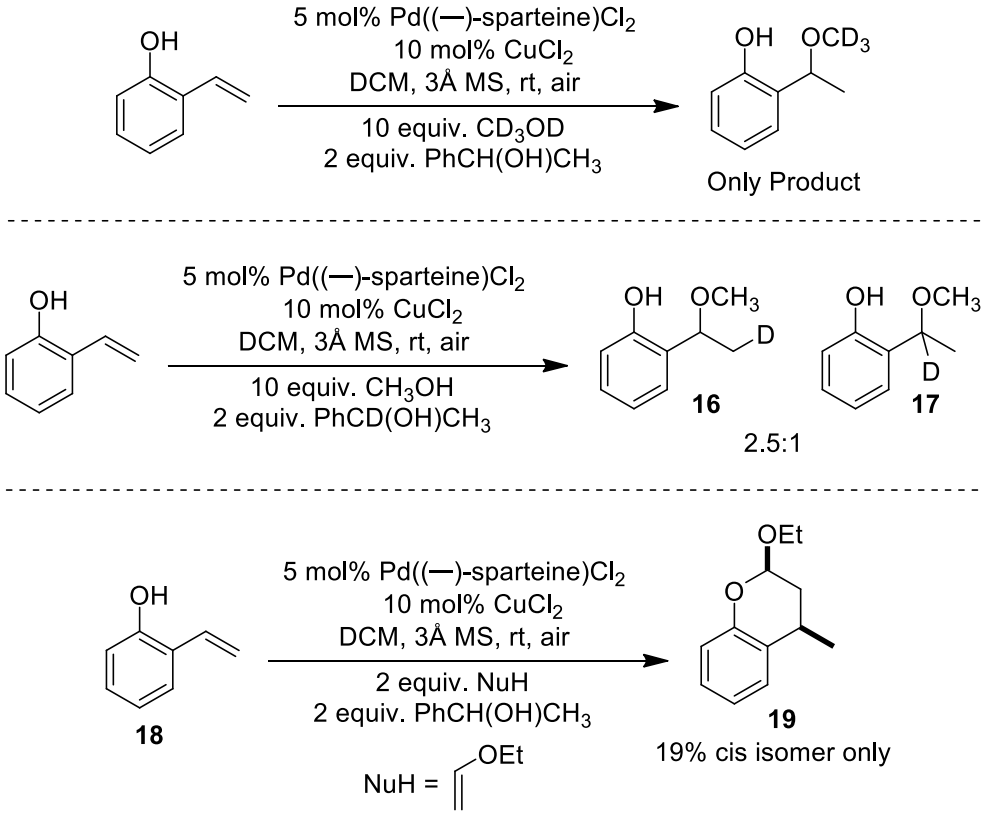

Figure 1.24. Evidence to support the proposed mechanism.

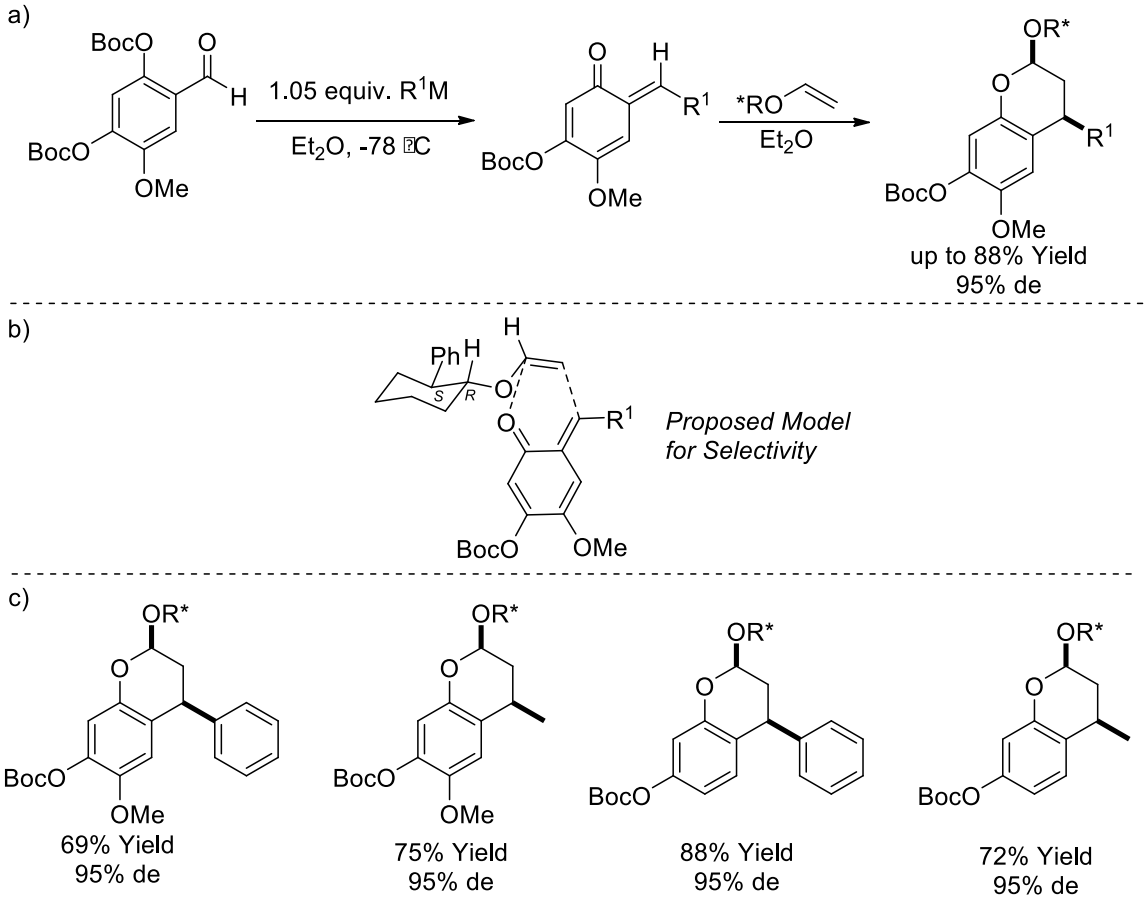

Figure 1.25. Diastereoselective reaction of chiral enol ethers with *o*-QM. Data from Pettus and coworkers.

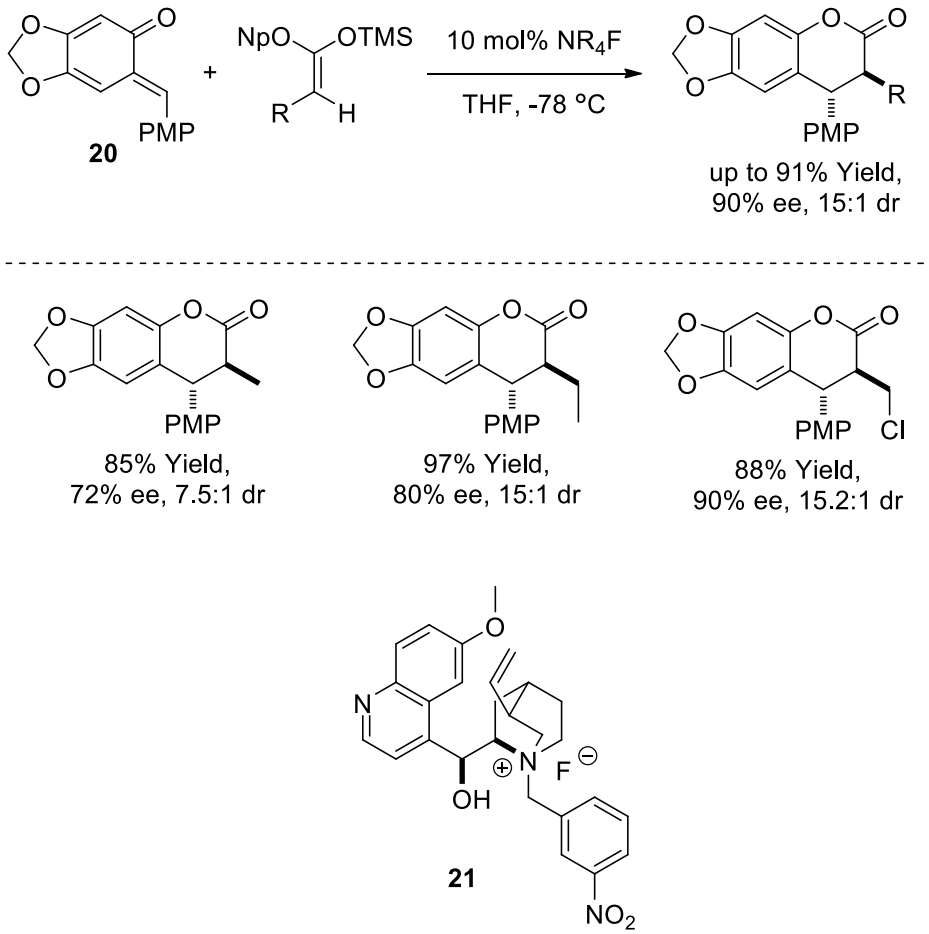

Figure 1.26. Enantioselective reaction of *o*-QM with ketene enolate using chiral ammonium fluoride pre-catalyst. Data from Lectka and coworkers.

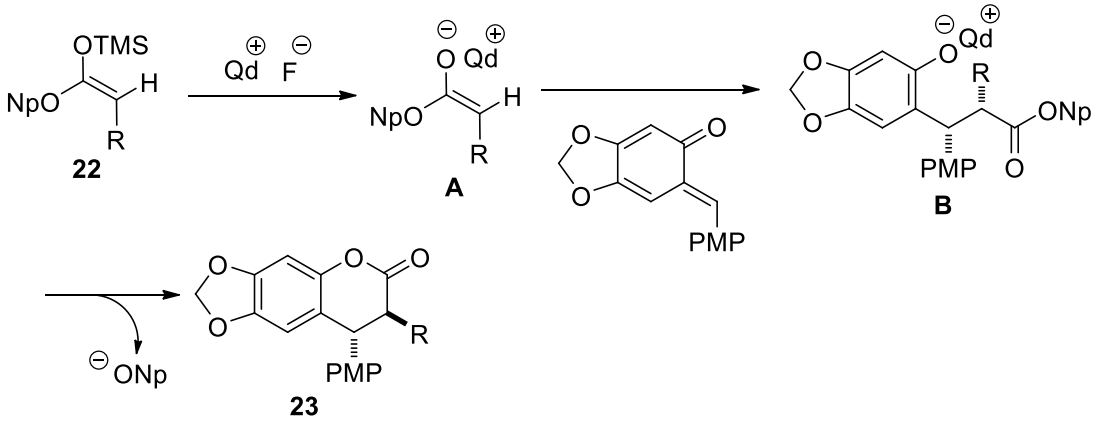

Figure 1.27. Proposed mechanism. Data from Lectka and coworkers.

In 2007, Sigman and coworkers reported an enantioselective Pd-catalyzed alkene difunctionalization reaction, which purportedly reacts via *o*-QM, with a relatively broad substrate scope of alcohols (Figure 1.28).[51] The use of (*S*)-*i*Pr-Quinox as a chiral ligand leads to the dialkoxylation product in excellent enantioselectivity and good diastereoselectivity. The major limitations of this process were the addition of identical nucleophiles across the alkene and the use of the nucleophile as the solvent.

Conclusion

Since its initial discovery, the chemistry of *o*-QM intermediates has made significant progress. Major advancements have been achieved in the characterization and synthesis of *o*-QM intermediates under mild conditions. *o*-QMs can be generated under acidic, basic as well as neutral conditions to react with various nucleophiles. This process has allowed for the efficient and rapid synthesis of phenol-containing natural products and chromane derivatives. Despite such advances, the reports of enantioselective functionalization of *o*-QM are only a handful, and this area holds potential for further

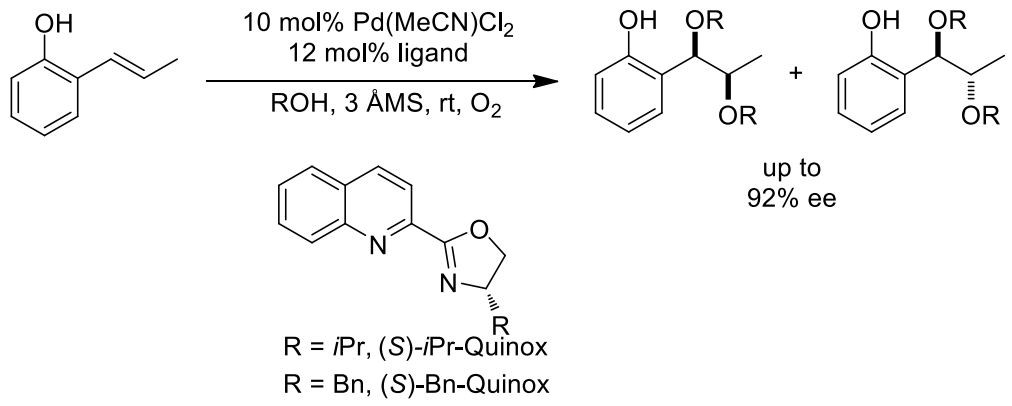

Figure 1.28. Enantioselective Pd-catalyzed dialkoxylation of vinyl phenols. Data from Sigman and coworkers.

development. This limitation and our discovery of a Pd-catalyst, which affords alkene difunctionalized products in excellent enantioselectivity provided the impetus to further pursue enantioselective alkene difunctionalization via the formation of an *o*-QM intermediate. In the following chapters, our findings are discussed in detail.

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CHAPTER 2

PALLADIUM-CATALYZED ENANTIOSELECTIVE DIFUNCTIONALIZATION OF SUBSTITUTED VINYLPHENOLS WITH ALCOHOLS AS EXOGENOUS NUCLEOPHILES

Introduction

Palladium(0)-catalyzed reactions have been widely used to successfully synthesize carbon-carbon and carbon–heteroatom bonds.[1-3] In recent years, substantial attention has been paid to oxidative palladium catalysis, which includes a wide variety of olefin functionalization reactions, such as the Wacker cyclization[4-8] and the oxidative Heck reaction.[9-10] These olefin functionalization reactions are proposed to proceed via nucleopalladation of an alkene with subsequent β-hydride elimination to give mono-functionalized product as shown in Figure 2.1. Though these reactions are useful, one of the limitations of mono-functionalization of alkenes is loss of chiral information during the β-hydride elimination step. However, in the case of alkene difunctionalization reaction such loss can be avoided, which makes development of a difunctionalization reaction very attractive.[11]

To achieve an enantioselective olefin difunctionalization reaction, several issues need to be addressed. First, the Pd-alkyl intermediate **B** should be render enantioenriched

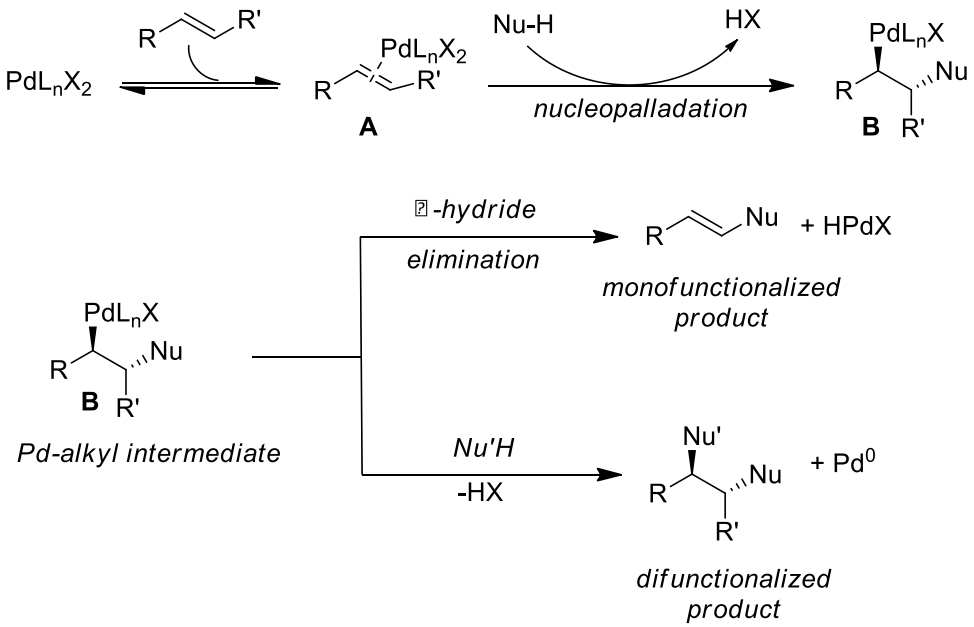


Figure 2.1.General mechanistic scheme.

by using an appropriate chiral ligand. More importantly, β-hydride elimination should be prevented to preserve the chiral information and allow for functionalization of the resulting Pd-alkyl intermediate. Therefore, it is necessary to develop a system in which the rate of the second functionalization step is greater than that of β-hydride elimination. This could potentially be achieved by either stabilizing the Pd-alkyl species (such as through Pd-π-allyl/benzyl stabilization) or by rapidly transforming the Pd-alkyl species into an intermediate suitable for further functionalization (such as oxidation of Pd^{II} to Pd^{IV}or *o*-QM formation).[11] In this chapter, recent examples of these two approaches will be discussed.

Background

Stabilization of Pd-alkyl Intermediate via Pd-π–allyl/benzyl Formation

The most commonly used substrates for preventing β–hydride elimination via formation of Pd-allyl intermediates are conjugated alkenes, such as dienes and styrenes. The Pd-alkyl species from dienes and styrenes form relatively stable Pd-π-allyl or Pd-π-benzyl complexes, respectively, thereby circumventing β-hydride elimination.

Bäckvall and coworkers have made significant contributions toward Pd-catalyzed diene difunctionalization reactions.[11-19] In 1981, they reported a noteworthy example of Pd-catalyzed diene diacetoxylation reaction, where either *cis* or *trans* difunctionalized products can be obtained (Figure 2.2).[13] Prior to this report such stereochemical control was difficult to achieve. It is proposed that coordination of Pd^{II} to the diene followed by *anti*-oxypalladation, results in formation of a Pd-π-allyl intermediate **B**. Nucleophilic attack of **B** by a second equivalent of acetate results in product formation with concomitant reduction of Pd. Benzoquinone is used as a terminal oxidant to regenerate Pd^{II} from Pd^{0}. Interestingly, the diastereoselectivity of the resultant product can be controlled based on chloride ion concentration. High [Cl^-] prevents pre-coordination of acetate to Pd, which results in intermolecular attack by acetate on **B** from the face opposite to palladium, leading to *cis*-**24**. In contrast, with low [Cl^-], intramolecular attack by a coordinated acetate occurs to form *trans*-**25**.

Later, Bäckvall and coworkers expanded the scope of this transformation to intramolecular processes, such as alkoxyacetoxylation, aminoacetoxylation, and aminochlorination reactions.[18] It should be noted that in the case of aminoacetoxylation

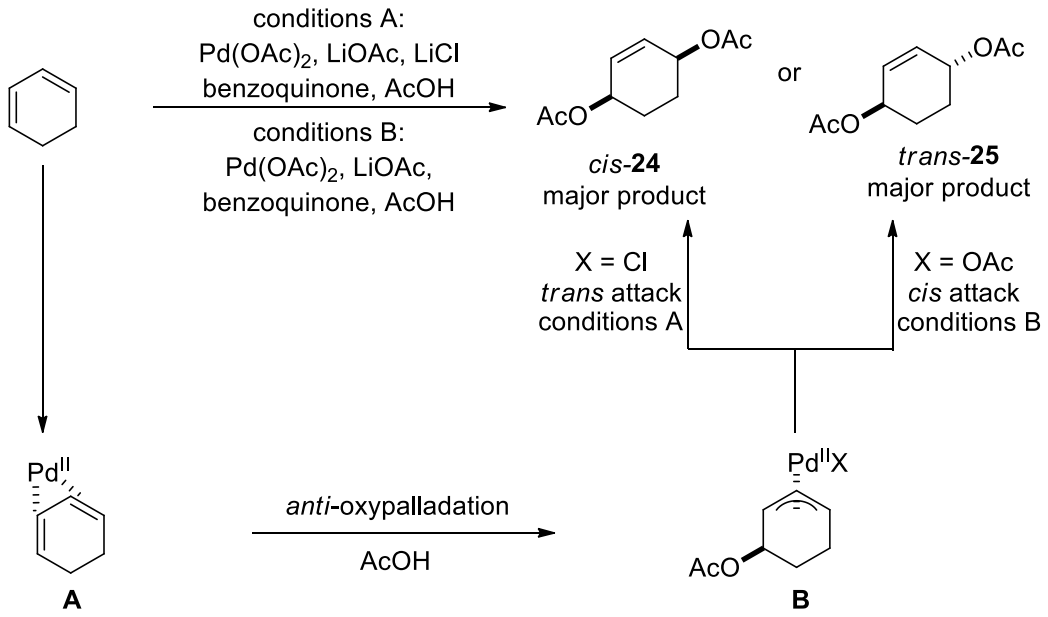


Figure 2.2. Pd-catalyzed 1,4-diacetoxylation of cyclic 1,3-dienes. Data from Bäckvall and coworkers.

reaction, a complete reversal in product stereochemistry was observed by using a catalytic amount of LiCl (Figure 2.3, compare reaction B and C). These reactions generally proceed with excellent diastereoselectivity and good yields.

Another elegant use of the Pd-π-allyl stabilization for difuctionalization of dienes was demonstrated by Booker-Milburn and coworkers (Figure 2.4).[20] Using this mode of Pd-alkyl stabilization, the authors were able to promote the diamination of various dienes in good yields. This reaction is proposed to proceed via nucleophilic attack of urea on the Pd-coordinated diene to yield the Pd-π-allyl intermediate **A**, which on subsequent intramolecular attack by the now tethered second nucleophile delivers the desired product.

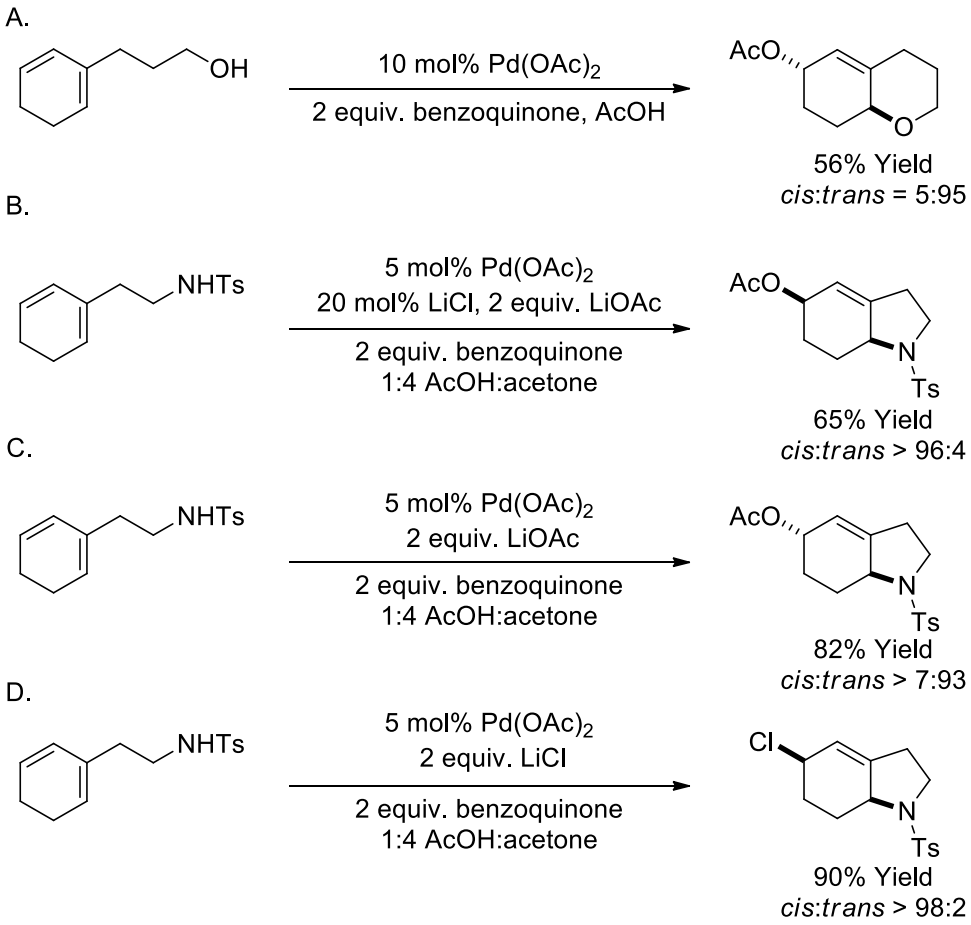


Figure 2.3. Pd-catalyzed intramolecular diene alkoxyacetoxylation, aminoacetoxylation, and aminochlorination reactions. Data from Bäckvall and coworkers.

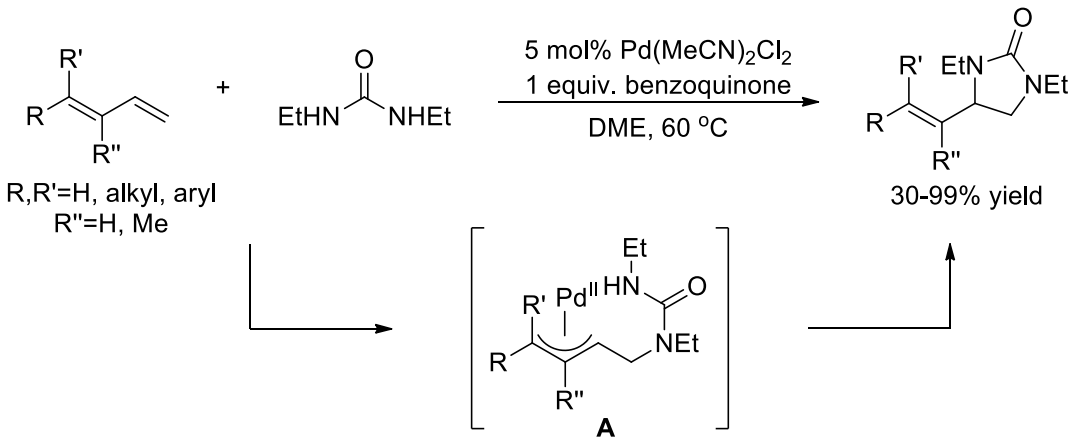


Figure 2.4. Pd-catalyzed diamination of dienes. Data from Lloyd-Jones and Booker-Milburn.

Recently, our group has reported Pd-catalyzed hydrofunctionalization and difunctionalization of styrenes with aryl stananes.[21] The reactions are likely proceeding through the Pd-π-benzyl intermediate, which is proposed to undergo transmetalation and reductive elimination to give the desired product (e.g., Figure 2.5). Later, the scope of the difunctionalization reaction was expanded to incorporate simple terminal alkenes as a substrate to give 1,1-difunctionalized products.[22] The proposed mechanism for 1,1-diarylation is shown in Figure 2.6, where initial transmetalation followed by insertion gives intermediate **A**. The intermediate **A** undergoes sequential β-hydride elimination and reinsertion to give Pd-π-benyl intermediate **B**, which proceeds to the observed product via a second transmetalation followed by reductive elimination.

Palladium-Catalyzed Alkene Difunctionalization Involving Pd^{II} to Pd^{IV} Oxidation

In recent years the use of high oxidation state Pd catalysis (Pd^{II}/Pd^{IV}) has grown significantly.[23-25] This increase in use of Pd^{IV} as a means to functionalize alkenes has several advantages over conventional Pd^{II}/Pd^{0} catalysis: 1) Pd^{IV} species are often resistant to β-H elimination processes, allowing diverse transformations of Pd^{IV} intermediates; 2) Pd^{IV} species undergo reductive elimination under relatively mild conditions; 3) In some cases, Pd^{II}/Pd^{IV} catalysis realizes transformations that are difficult to achieve by Pd^{II}/Pd^{0} catalyzed reactions.

A general catalytic cycle for Pd^{II}/Pd^{IV} catalysis is shown in Figure 2.7. The coordination of Pd^{II} with an alkene followed by nucleophilic attack of a suitable nucleophile results in the Pd-alkyl intermediate **B**. Pd^{II}-alkyl intermediate **B** then

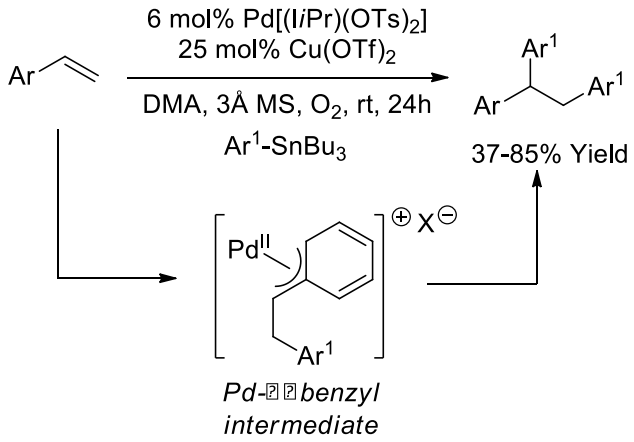


Figure 2.5. Pd-catalyzed 1,2-diarylation of styrenes. Data from Sigman and coworkers.

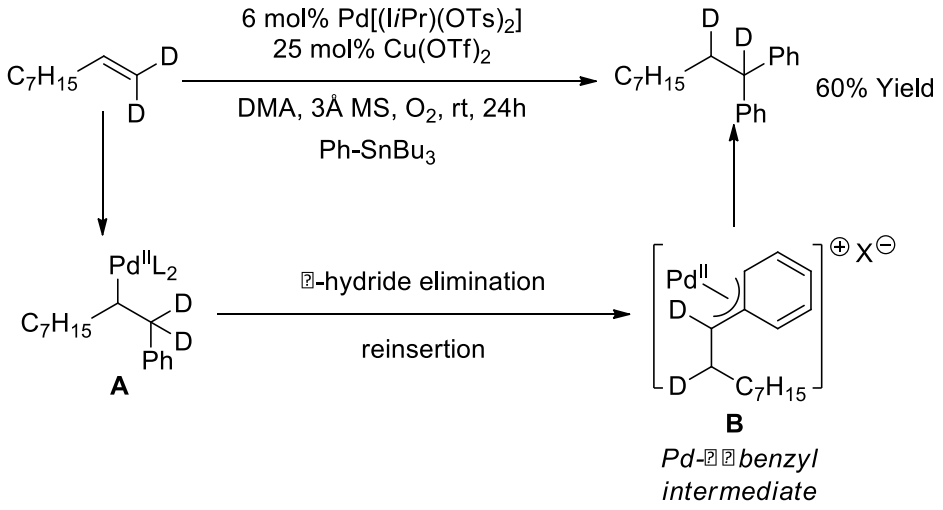


Figure 2.6. Pd-catalyzed 1,1-difunctionalization of simple alkenes. Data from Sigman and coworkers.

undergoes oxidation to Pd^{IV}-alkyl intermediate **C**, which subsequently reacts with an equivalent of nucleophile to give the difunctionalized product. The second functionalization can proceed through two possible pathways: 1) reductive elimination of C-Nu from Pd^{IV}, resulting in retention of stereochemistry, or 2) nucleophilic attack of an external nucleophile with Pd^{II} as the leaving group, resulting in inversion of stereochemistry.

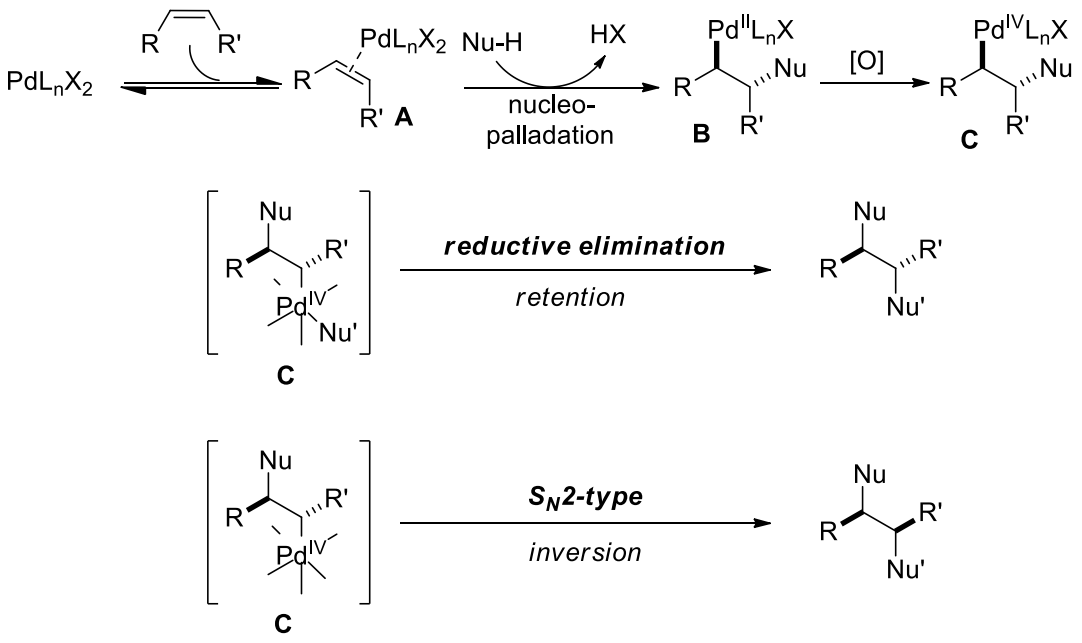


Figure 2.7. Proposed mechanism for Pd-catalyzed reaction invoking a Pd^{IV} intermediate.

In 2005, Sorenson and coworkers reported an intramolecular aminoacetoxylation of alkenes using Pd^{II}/Pd^{IV} catalysis (Figure 2.8a). [26] They used $PhI(OAc)_2$ as an oxidant to oxidized the Pd^{II}-alkyl species to the Pd^{IV}-alkyl intermediate. Soon after, Muñiz and coworkers reported the use of Pd^{II}/Pd^{IV} catalysis for intramolecular diamination of unactivated alkenes using *o*-alkenyl-substituted ureas as substrates (Figure 2.8b).[27-29] In addition, Stahl and co-workers reported the diastereoselective intermolecular aminoacetoxylation of terminal alkenes with phthalimide as the nitrogen nucleophile (Figure 2.8c).[30] Sanford and co-workers utilized a similar strategy for the diastereoselective construction of substituted tetrahydrofurans through aminooxygenation of alkenes (Figure 2.8d).[31]

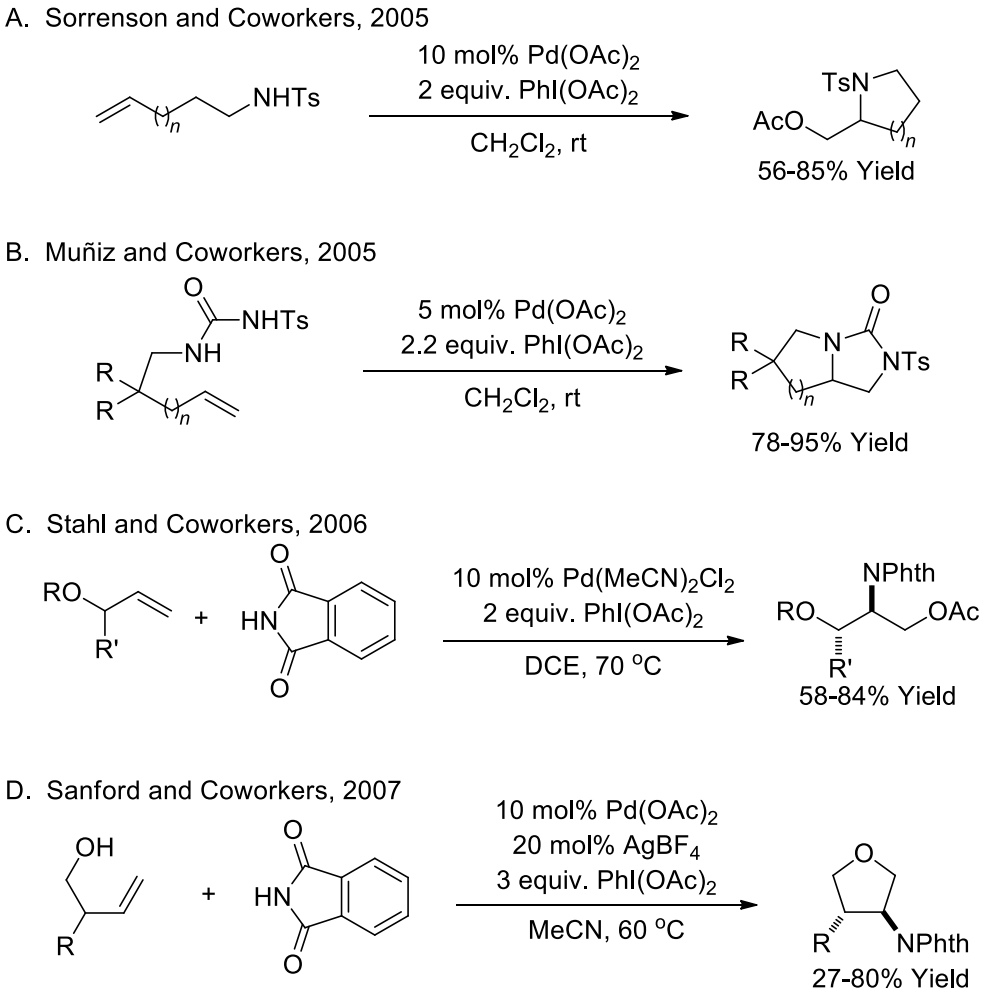


Figure 2.8. Early examples of Pd^{IV} in alkene difunctionalization reactions.

Another elegant use of Pd^{II}/Pd^{IV} catalysis was reported by Song and Dong for diacetoxylation of alkenes (Figure 2.9).[32] In this chemistry, the authors used $PhI(OAc)_2$ as the preferred oxidant to give a diacetoxylation product **26** in good yield and excellent diastereoselectivity. However, recently Gade and coworkers reported that the TfOH, generated from the first catalytic turnover, is the active catalyst in this transformation.[33] Later, Jiang and coworkers reported a diacetoxylation of alkenes using O_2 as the sole oxidant.[34] In 2010, Jung and coworkers reported the diacetoxylation of alkenes in the

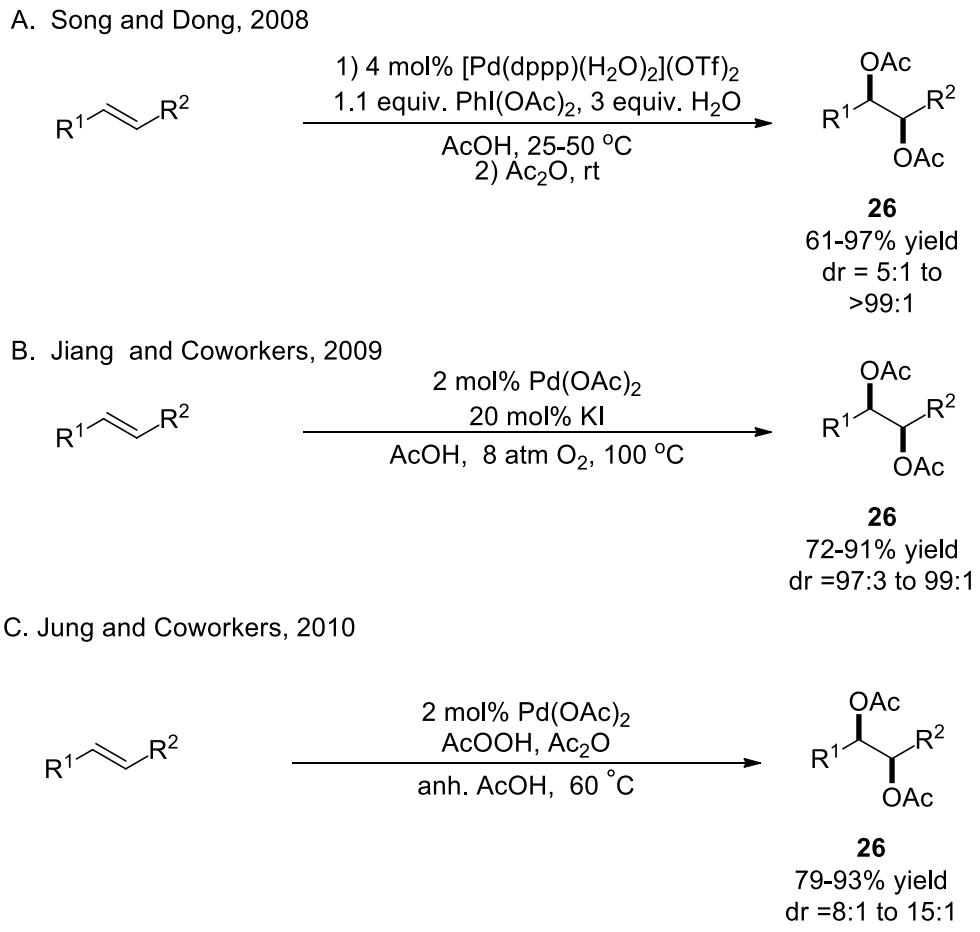


Figure 2.9. Pd-catalyzed alkene diacetoxylation reactions.

presence of peracetic acid and acetic anhydride to produce diacetates in good yields and diastereoselectivity.[35]

Electrophilic fluorinating reagents like N-fluorobenzenesulfonimide (NFSI) can effectively oxidize the Pd^{II}-alkyl intermediates to Pd^{IV}-alkyl intermediates (Figure 2.10). Michael and coworkers reported the use of NFSI for Pd-catalyzed diamination of simple alkenes. [36-37] NFSI acts as both the oxidant and nitrogen source in the alkene diamination reaction.[36] Interestingly, when aromatic solvents are used, the aminoarylation was observed predominantly (Figure 2.10b). This is proposed via attack of an aromatic group

to the electrophilic Pd^{IV}-species through the electrophilic aromatic substitution mechanism.[37] Recently, Liu and coworkers utilized NFSI as an effective oxidant in their intermolecular flouroamination of alkenes. Here, NFSI acts as the source of both fluorine anion and nitrogen nucleophile (Figure 2.10c).[38]

As described in Chapter 1, our group has developed a distinctive method for the difunctionalization of vinyl phenols via conversion of a Pd-alkyl intermediate to an *o*-QM as a latent electrophile. Though these reactions are mechanistically intriguing, they have limited substrate scope. Recently, we have reported highly enantioselective difunctionalization of vinyl phenols with alcohols as nucleophiles.[39] The major limitation of this approach is the addition of identical nucleophiles across an alkene. To overcome this, we envisioned a difunctionalization reaction, where one of the nucleophiles is

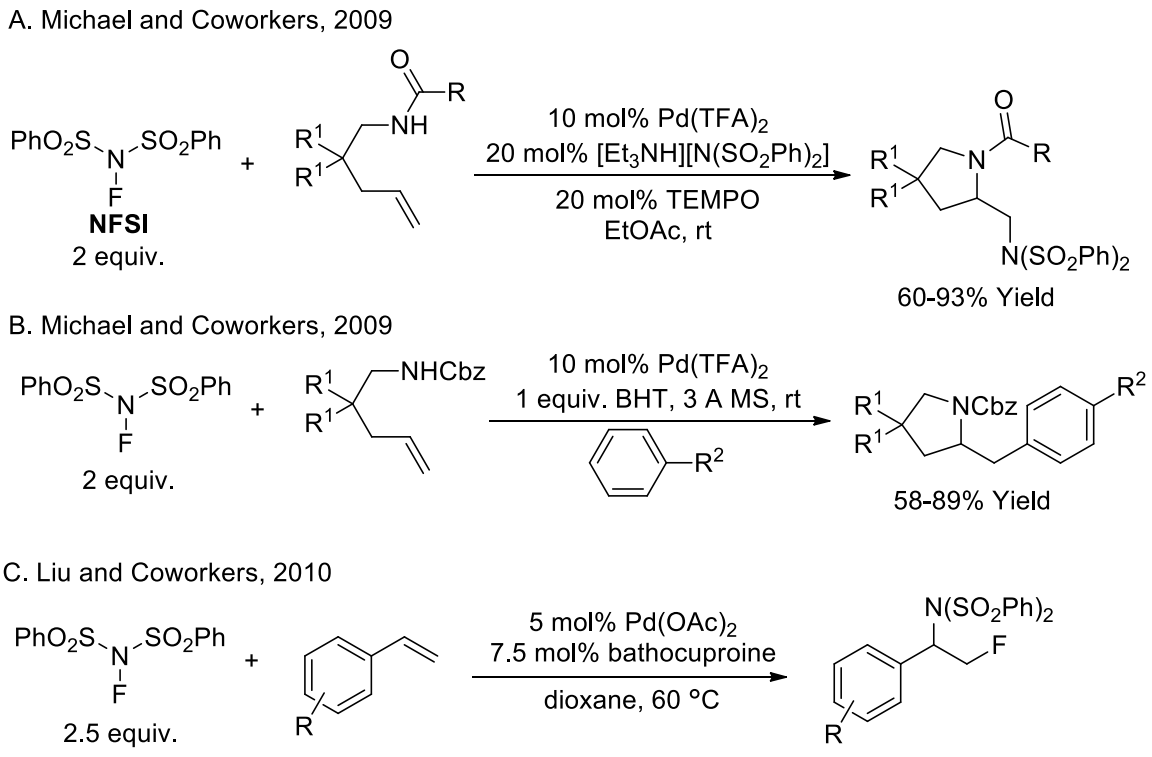


Figure 2.10. Alkene difunctionalization using NFSI as an oxidant.

incorporated into the starting material as shown in Figure 2.11. We hypothesized that this class of substrates would first undergo nucleopalladation in an intramolecular fashion to give the palladium alkyl species **A**. This would subsequently undergo quinone methide formation **B**, followed by attack of an external nucleophile, to yield product. These proposed substrates would allow us to functionalize substituted vinyl phenols with two distinct nucleophiles to give substituted heterocycles, which are prominent structures in pharmaceutically interesting compounds and natural products. The remainder of this chapter is devoted to a detailed discussion of our findings.

Reaction Development and Optimization

To test our hypothesis, we synthesized substrates containing alcohols that can act as intramolecular nucleophiles. Our strategy for preparing these substrates can be

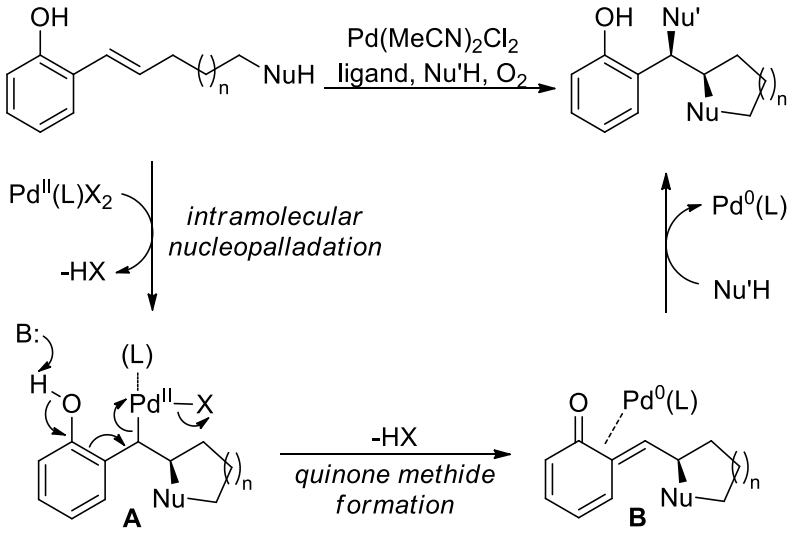


Figure 2.11. Mechanistic proposal for difunctionalization of vinyl phenols with two different nucleophiles.

divided into two general routes as shown in Figure 2.12. The Wittig salt **27** was synthesized by the reaction of commercially available ethyl-4-bromobutanoate with triphenylphosphine. Wittig salt **27** was then subjected to the reaction with salicylaldehyde **28**, in the presence of potassium *tert*-butoxide as base to yield alkene **29**. This was subsequently treated with either MeMgBr or $LiAlH_4$ to give products **30** and **31**, respectively. Vinyl phenols **36** and **39** were synthesized using a Sonogashira coupling route. The Sonogashira coupling between aryl iodide **32** and alkyne **33** gave compound **34** in excellent yield. Alkyne **34** was then converted to the alkene **35** via a Pd-catalyzed hydrogenation reaction and subsequently deprotected to give compound **36**.

Optimization of reaction conditions and evaluation of substrate scope were conducted in collaboration with former graduate student Dr. Katrina Jensen. Initial evaluation of **30** under conditions similar to the intermolecular dialkoxylation gave the desired product in good enantioselectivity but in very low yield and with a significant number of unidentified side products (Table 2.1, entry 1). During the optimization of the intermolecular dialkoxylation reaction, it was observed that a catalytic amount of $CuCl_2$ accelerates this transformation and generally leads to better chemoselectivity. Unfortunately, during this study Dr. Yang Zhang also observed decreased enantioselectivity with an increased copper loading (Table 2.2).[39] We believe this decrease in enantioselectivity is due to the ligand exchange between copper and palladium. Therefore, a pre-formed copper complex was used in order to prevent ligand exchange and resulting decrease in enantioselectivity. Excitingly, an increase in product yield and enhanced chemoselectivity was observed without a significant decrease in

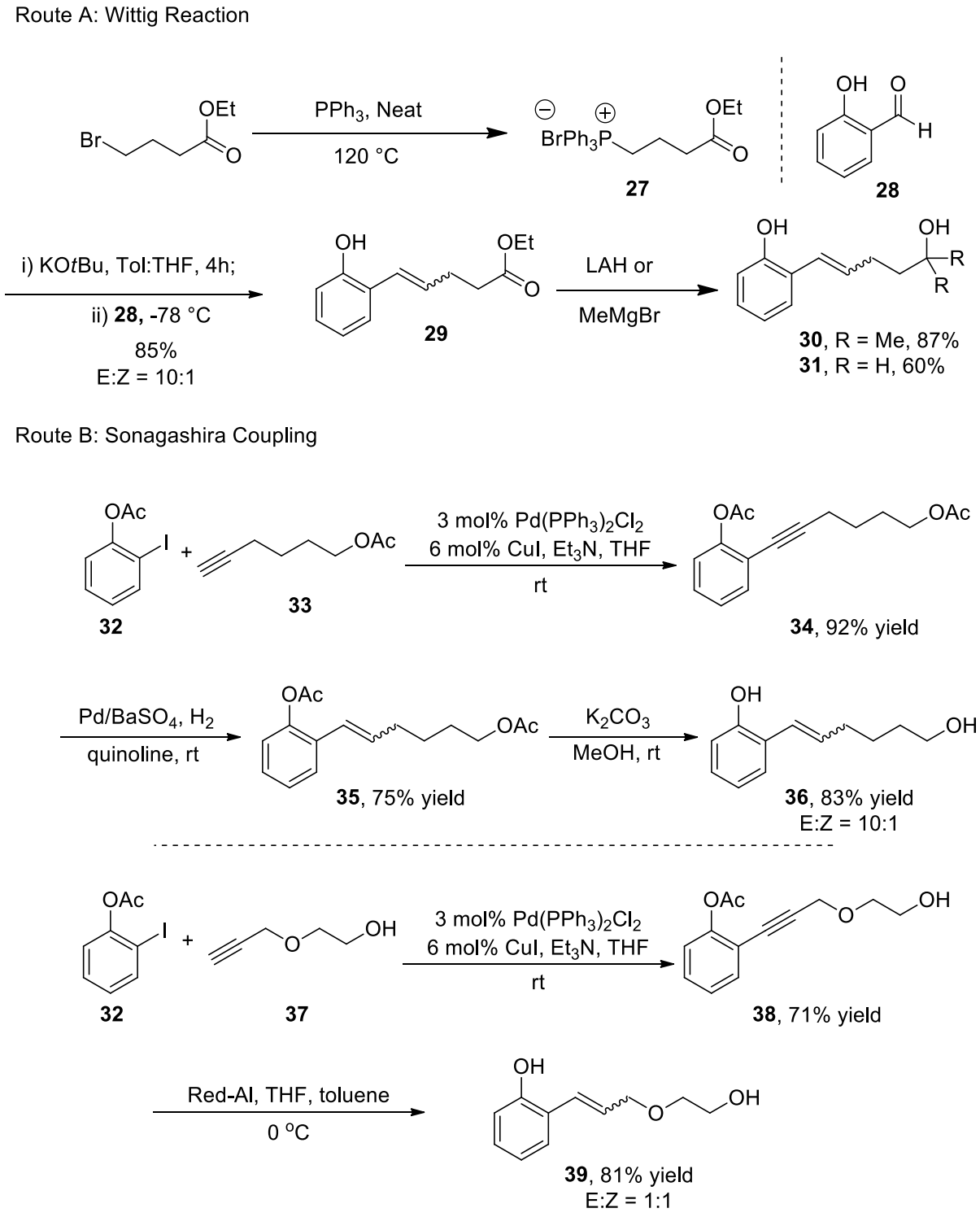
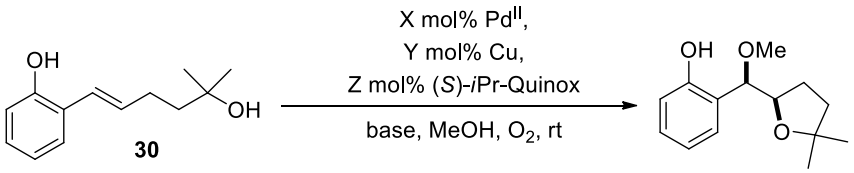


Figure 2.12. Two different approaches to substrate synthesis.

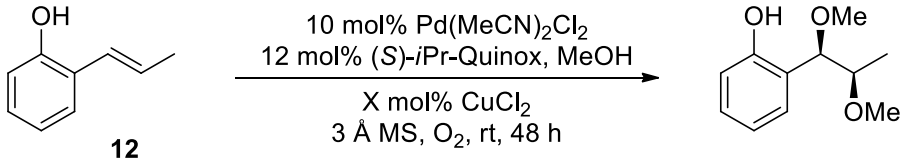
Table 2.1. Initial optimization.



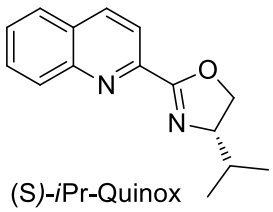
Entry	X	Y	Z	base	time	%yield[a]	er[b]
1[c]	10 mol% $Pd(MeCN)_2Cl_2$	--	12%	25 mol% KOtBu	42 h	10	90:10
2[c]	10 mol% $Pd(MeCN)_2Cl_2$	20 mol% Cu(*i*Pr-Quinox)Cl_2	2%	25 mol% KOtBu	1 h	70	89.5:10.5
3[c]	5 mol% Pd(*i*Pr-Quinox)Cl_2	15 mol% Cu(*i*Pr-Quinox)Cl_2	3%	25 mol% KOtBu	1 h	20	92:8
4	5 mol% Pd(*i*Pr-Quinox)Cl_2	15 mol% Cu(*i*Pr-Quinox)Cl_2	3%	25 mol% KOtBu	1 h	60	93.5:6.5
5	5 mol% Pd(*i*Pr-Quinox)Cl_2	12 mol% Cu(*i*Pr-Quinox)Cl_2	2%	25 mol% KOtBu	1 h	21	88.5:11.5
6	5 mol% Pd(*i*Pr-Quinox)Cl_2	12 mol% Cu(*i*Pr-Quinox)Cl_2	2%	25 mol% $NaHCO_3$	1 h	63	92:8

(a) Measured by GC using an internal standard. (b) ee determined by gas chromatography using a chiral column. Reaction performed at 0.1 mmol. (c) 3 Å MS was used.

Table 2.2. Detrimental effect of copper on enantioselectivity in the Pd-catalyzed alkene dialkoxylation reaction.



mol% $CuCl_2$	% GC yield	% ee	er
0	67	82	91:9
2.5	80	72	86:14
5	78	59	80:20
10	81	26	63:37
20	88	10	55:45

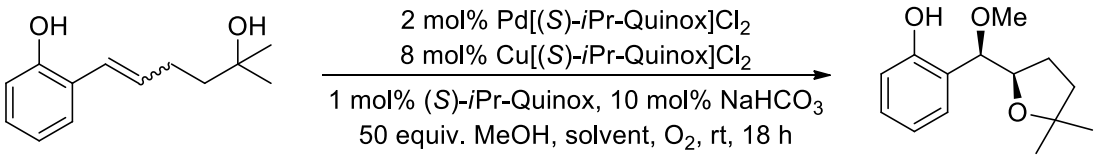


enantioselectivity (Table 2.1, entry 2). Reduced catalyst loading resulted in lower yield (Table 2.1, entry 3), while removal of molecular sieves resulted in an unexpected increase in product yield. (In the case of intermolecular dialkoxylation, molecular sieves were beneficial) (Table 2.1, compare entries 3 and 4). By changing the base from KO*t*Bu to $NaHCO_3$, we were able to recover the yield loss that resulted from lowering $CuCl_2$ loading (Table 1.1, compare entries 5 and 6). With the virtue of using a common solvent for all nucleophiles, other solvents were tested with 50 equivalents of MeOH as a nucleophile. Enantioselectivity and selectivity of product formation were found to be greatly solvent dependent. As a crude measure of this selectivity, GC product peak area was compared to all other peak areas (besides starting material). After this systematic screening of solvents, THF and toluene were found to give better enantioselectivity and chemoselectivity (Table 2.3). Thus, these solvents were chosen for further pursuits. Toluene, THF or a 1:1 mixture of toluene:THF each allowed for product formation with high enantioselectivity, short reaction times, and good yield (Table 2.4, entries 1-3) Furthermore, in situ-formed complexes gave results similar to those from the preformed complexes under these reaction conditions. Employment of Cu^{I} in place of Cu^{II} resulted in shorter reactions times, likely due to an effect of overall $[Cl^{-}]$ (Table 2.4, entry 4).

Evaluation of Substrate Scope

Having optimized conditions in hand, the scope of the sequential intra- and intermolecular dialkoxylation reaction was evaluated. The scope of this reaction is divided in two parts: 1) scope of intermolecular nucleophiles and 2) scope of intramolecular nucleophiles.

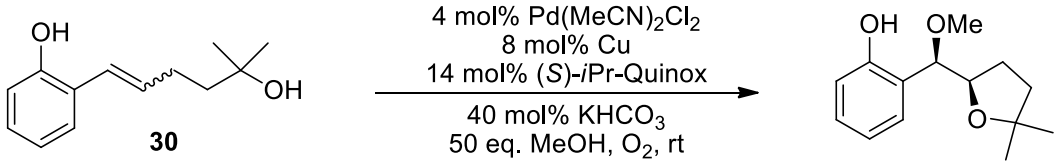
Table 2.3. Co-solvent assessment.



entry	solvent	ee	selectivity[a]
1	*t*BuOH	85%	0.1:1
2	*t*AmylOH	92%	0.4:1
3	toluene	94%	3.8:1
4	THF	93%	4:1
5	DCE	86%	1.6:1
6	CH_2Cl_2	73%	3:1
7	DMA	61%	5:1
8	DMF	60%	3.5:1
9	trifluorotoluene	76%	2:1
10	xylenes	91%	1.4:1
11	benzene	89%	3.2
12	dioxane	95%	2:1[b]
13	DME	95%	2:1
14	TBME	83%	5:1

[a]This is a ratio of area of product peaks: area of all other byproduct peaks observed by GC analysis [b]41 h

Table 2.4. Final optimization.



entry	solvent	Cu	time	%conv[a]	%yield[a]	ee[b]	er[b]	dr[b]
1	THF	$CuCl_2$	2 h	79	54	96%	98:2	7.8:1
2	toluene	$CuCl_2$	2 h	96	68	94%	97:3	5.1:1
3	1:1 THF:toluene	$CuCl_2$	5 h	100	67	94%	97:3	6.7:1
4	1:1 THF:toluene	CuCl	2 h	99	80	95%	98:2	8.9:1

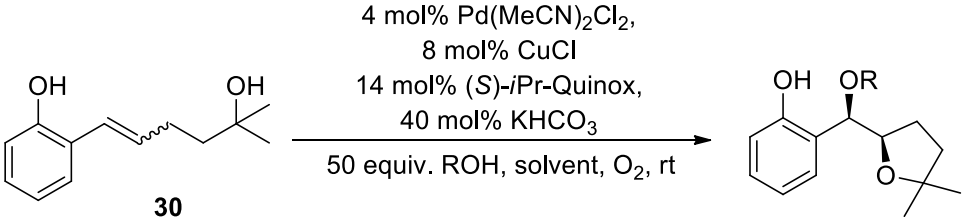
Reactions run on 0.1 mmol scale with [**30**] = 0.1 M. [a]Determined by GC analysis using an internal standard. [b]Determined by GC with a column equipped with a chiral stationary phase.

Intermolecular Nucleophiles

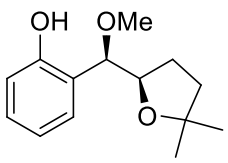
As discussed above, since the 1:1 toluene:THF mixture and toluene alone were found to provide good yield and excellent enantioselectivity of the desired product, both solvent systems were tested for alcohol nucleophiles (Table 2.5). In addition to methanol, other simple alcohols also provided the desired difunctionalized product in good yield and excellent enantioselectivity. This is noteworthy because primary alcohols containing a β-hydrogen are known to undergo palladium-catalyzed alcohol oxidation much more readily than methanol. Thus, it was important to confirm that primary alcohols can be used as exogenous nucleophiles under these conditions. In some cases, the use of toluene as solvent was found to give slightly improved yields. Ethers, with the potential for deprotection, are formed using benzyl alcohol and trimethylsilylethanol, with the latter giving an excellent er of 99:1 (**47**). A relatively complex chiral alcohol, (─)-myrtenol, was employed successfully (**48**), demonstrating the potential to couple two chiral partners.

When more polar nucleophiles like H_2O and ethylene glycol (EG) were subjected to the optimized conditions, they did not provide any desired product. This was proposed to be because of low miscibility of these nucleophiles in nonpolar solvents. To improve the solubility of these nucleophiles, hindered alcohols such as *t*-BuOH and *t*-AmylOH were evaluated as solvents. In both solvents, using 50 equivalent of H_2O as the nucleophile, product formation was observed in good yield with excellent enantioselectivity. However, because *t*-BuOH solidifies at 24 °C, *t*-AmylOH was chosen as a preferred solvent. In *t*-AmylOH, both H_2O and ethylene glycole gave good yield of

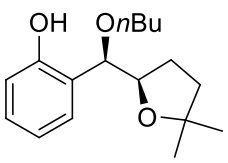
Table 2.5. Scope of exogenous alcohol nucleophiles.



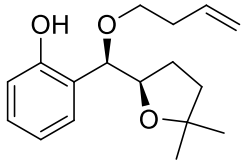
30



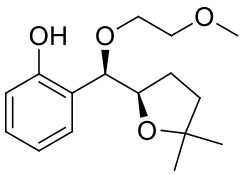
41
72% yield
1:1 THF:toluene, 3 h
97:3 er; 10:1 dr



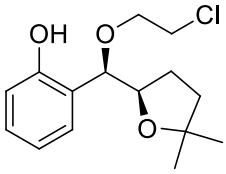
42
63% yield
toluene, 12 h
96:4 er; 5:1 dr



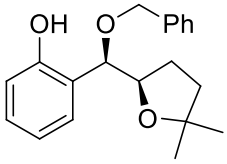
43
57% yield
toluene, 12 h
96:4 er; 4:1 dr



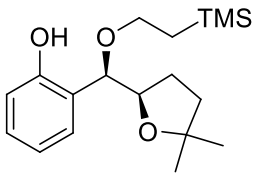
44
53% yield
1:1 THF:toluene,12 h
97:3 er; 9:1 dr



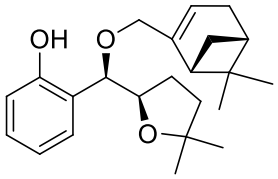
45
60% yield
toluene, 12 h
94:6 er; 5:1 dr



46
51% yield
1:1 THF:toluene, 16 h
97:3 er; 6:1 dr



47
64% yield[a]
toluene, 16 h
99:1 er; 6:1 dr



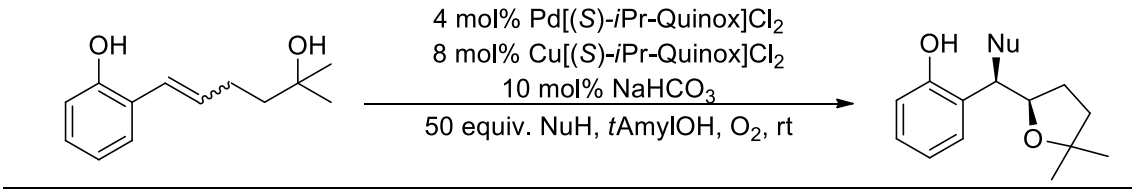
48
55% yield[a]
toluene, 12 h
10:1 dr

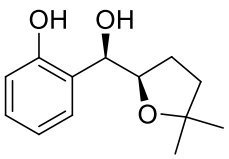
Isolated yield on 0.50 mmol scale. er for major diastereomer.
[a]25 equiv. of NuH.

the desired product with excellent enantioselectivity (Table 2.6). Moreover, NaN_3 was also found to be an effective nucleophile, demonstrating that an exogenous nitrogen nucleophile is viable. While low diastereoselectivity is observed, the diastereomers of **51** are readily separated. No improvement in product yield or enantioselectivity was observed by changing the azide anion source to *tetra*-butylammonium azide (TBAA) or $TMSN_3$. Other nucleophiles that did not lead to the difunctionalized products are shown in Figure 2.13.

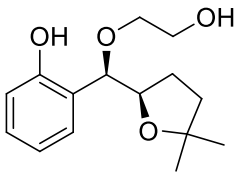
As discussed in Chapter 1, *o*-QMs are known to undergo inverse electron demand Diels-Alder reactions with electron rich enol ethers. Thus, to evaluate the compatibility of enol ethers as nucleophiles in our difunctionalization method, we (in collaboration with Dr. Katrina Jensen) subjected enol ether **52** to reaction conditions with a standard substrate **30** (Figure 2.14). To our delight, chromane **53** was obtained in good yield and excellent enantioselectivity and diastereoselectivity. The primary alcohol substrate **31** also gave product **54** with excellent stereoselectivity. It should be noted that in the above

Table 2.6. Scope of polar exogenous nucleophiles

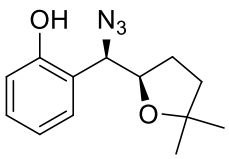




49
63% yield
24 h
98:2 er; 5:1 dr



50
59% yield
24 h
95:5 er; 9:1 dr



51
51% yield[a]
48 h
92:8 er; 1.4:1 dr

Isolated yield on 0.50 mmol scale. er for major diastereomer [a]2 equiv. of NaN_3, 30 °C.

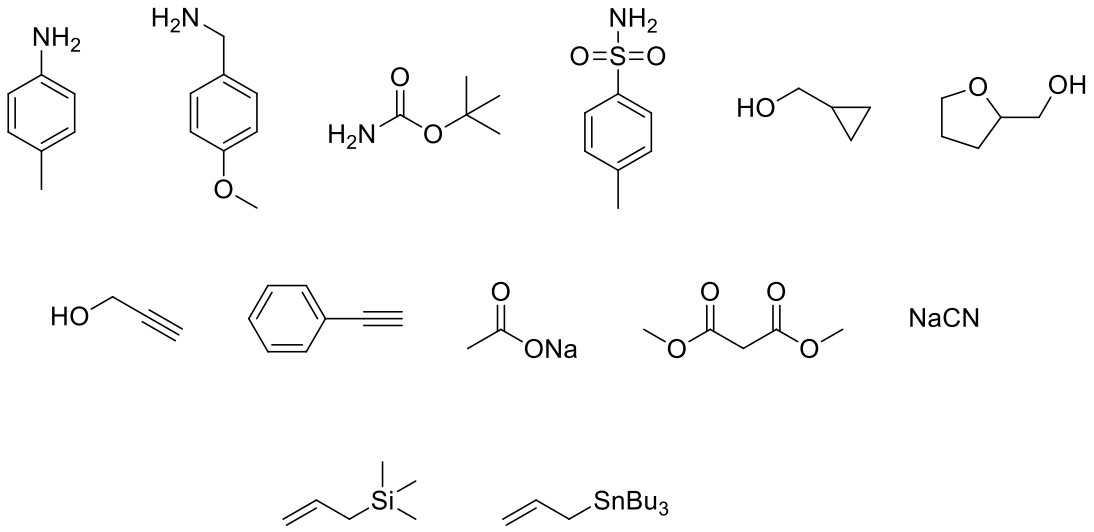


Figure 2.13. Nucleophiles that failed to yield the desired product.

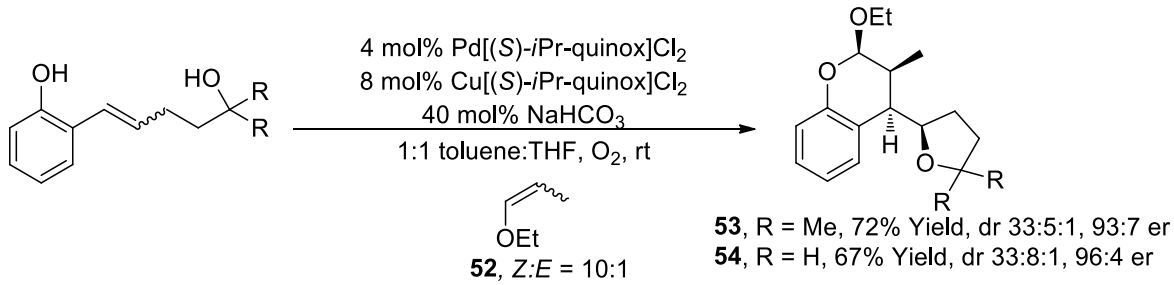


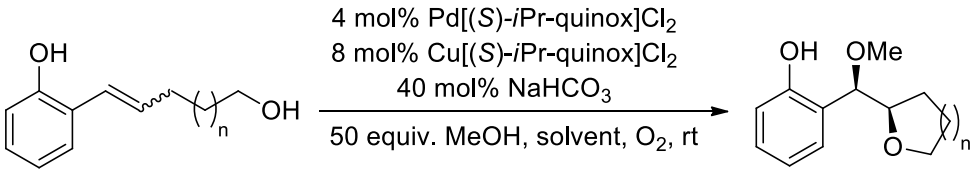
Figure 2.14. Inverse electron demand Diels-Alder reaction with enol ether **52**.

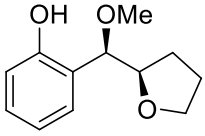
mentioned reaction, three new bonds with four contiguous chiral centers were constructed in a single step. This clearly demonstrates the power of this method to construct relatively complex frameworks from a simple substrate, in a single step.

Intramolecular Nucleophiles

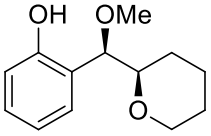
In examining other ring systems that could be accessed, it was found that five and six membered rings could be successfully formed from tethered alcohol nucleophiles (Table 2.7). In addition to the tertiary alcohol substrates, the primary alcohols **31** and **36**

Table 2.7. Scope of intramolecular nucleophiles.

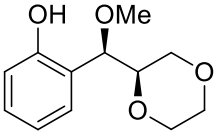




55
68% yield
1:1 THF:tol, 7 h
95:5 er; 10:1 dr



56
50% yield
1:1 THF:tol, 24 h
95:5 er; 6:1 dr



57
30% yield[a]
toluene, 24 h
92:8 er; 6:1 dr

Isolated yield on 0.50 mmol scale. er for major diastereomer. [a]1 eq. $NaHCO_3$

also cyclized to the corresponding tetrahydrofuran **55** and tetrahydropyrane **56** with high enantio- and diastereoselectivity. A 1,4-dioxane can also be accessed in modest yield and good enantioselectivity.

Product Derivatization

While the phenol moiety is a mechanistic requirement for *o*-QM formation, it also provides a handle for further derivatization of products. We envisioned that oxidation of the phenol to a carboxylic acid would provide the basic building block for further functionalization. However, when compound **55** was treated with ozone (O_3), no desired product formation was observed. Ru-catalyzed oxidation of arenes to carboxylic acids is well documented in the literature,[40-41] thus it was examined for oxidation of **55**. After significant optimization of the reaction conditions, we arrived at these optimal conditions: 10 mol% $RuCl_3$ and 10 mol% $NaIO_4$ in a $MeCN:CCl_4:H_2O$ (2:2:3) solvent system

(Figure 2.15). Under these conditions, **55** gave the desired product **58**, in 43% yield with no deterioration of diastereoselectivity or enantioselectivity.

Another useful method for functionalization of phenols is via dearomatization. This is a very powerful method to provide synthetically useful *p*-benzoquinone ketals.[42] Thus, compound **41** and **55** were treated with $PhI(OAc)_2$ in MeOH to give **59** and **60** as the corresponding products in good yields (Figure 2.16).

Determination of Product Stereochemistry

The relative stereochemistry between newly formed stereocenters was determined by X-ray analysis of compound **41** (Figure 2.17). Mosher ester analysis was used to determine the absolute stereochemistry (Figure 2.18).[43-44] Product **41,** which was obtained using water as the exogenous nucleophile was used in this analysis. Methyl protection of the phenol followed by coupling with each enantiomer of Mosher's acid gave the diastereomeric Mosher esters **62** and **63.** Based on chemical shift analysis and in combination with the crystal structure data, the absolute stereochemistry was assigned as (*R*,*R*).

Conclusion

We have developed a highly enantioselective Pd-catalyzed alkene difunctionalization reaction involving the addition of two distinct nucleophiles.[45] This

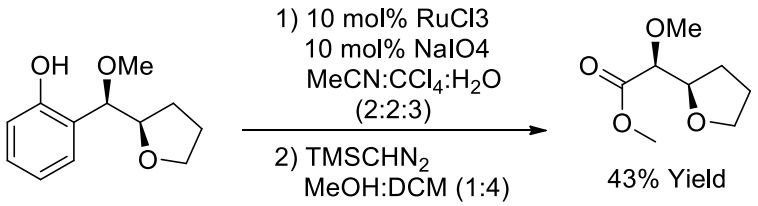


Figure 2.15. Ru-catalyzed oxidation of phenol to carboxylic acid.

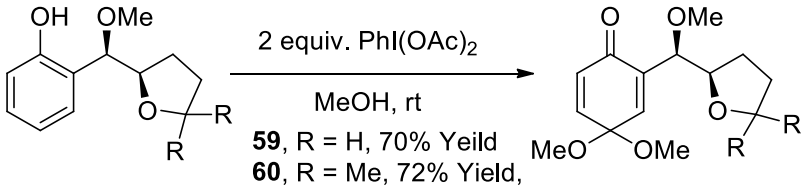


Figure 2.16. Dearomatization of phenol.

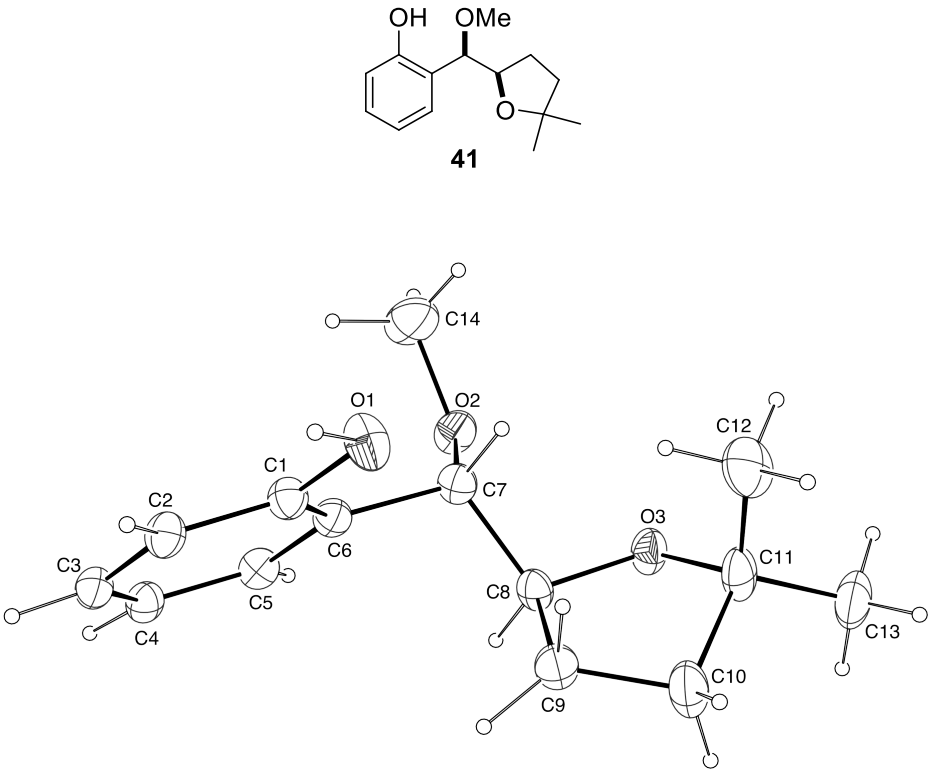


Figure 2.17. X-ray crystal structure of product **41.**

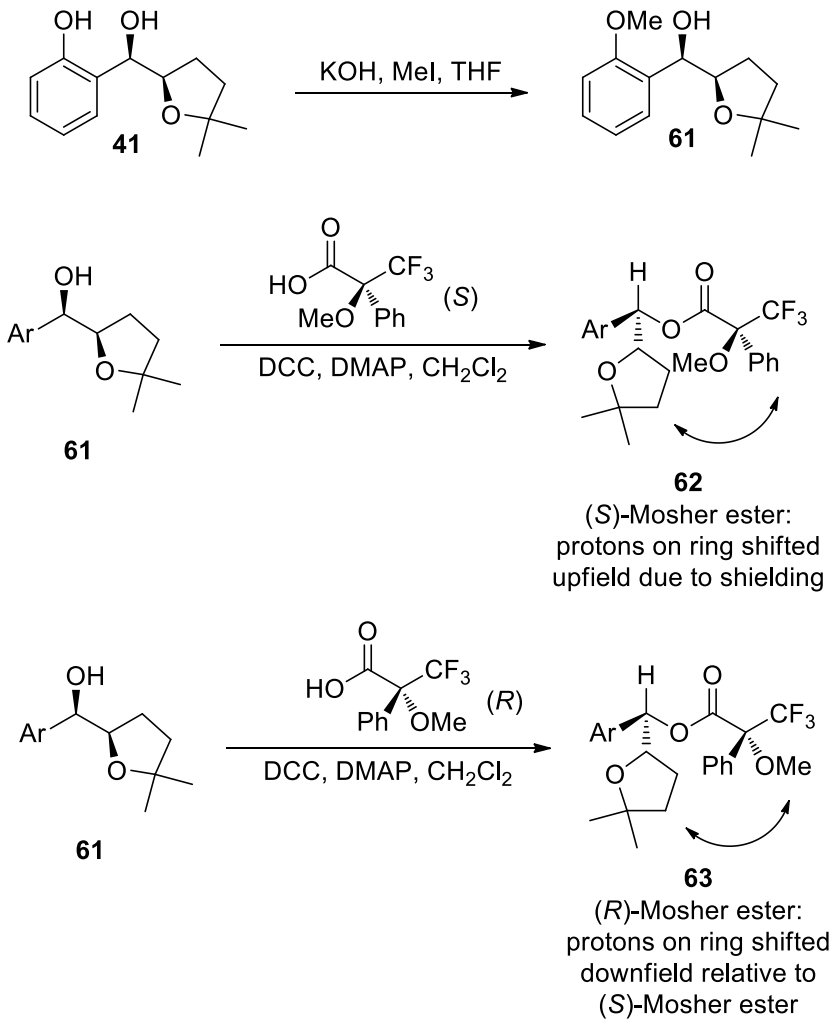


Figure 2.18. Mosher ester analyis.

process allows for the formation of complex chiral molecules from relatively simple starting materials. A key step in the optimization of the reaction conditions was the use of a ligated copper complex as a co-catalyst, which drastically improved reaction rate and yield, with no detrimental effect on enantioselectivity. Furthermore, the optimized conditions allowed for the use of exogenous nucleophiles other than solvent. In evaluating the scope of the reaction, alcohols, water, and sodium azide were found to add successfully as exogenous nucleophiles.

Experimental

General Considerations

Unless otherwise noted, all reactions were performed under a nitrogen atmosphere with stirring. Toluene, CH_2Cl_2, dichloroethane and THF were dried before use by passing through a column of activated alumina. Methanol was distilled from magnesium methoxide. Et_3N was distilled from CaH_2. 3Å molecular sieves were powdered and activated by flame heating under vacuum (ca. 3 min). *n*-Butanol, *n*-Butenol and etheleneglycol monomethylether were purified by distillation from $MgSO_4$. All other reagents were purchased from commercial sources and used without further purification. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, or stained either with potassium permanganate, *p*-anisaldehyde, phosphomolybdic acid, or ninhydrin. Flash column chromatography was performed with EcoChrom MP Silitech 32-63D 60Å silica gel, slurry packed with solvents indicated in glass columns. Nuclear magnetic resonance spectra were acquired at 300, 400, or 500 MHz for ^1H, and 75, 100,

or 125 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million downfield relative to the line of $CHCl_3$ singlet at 7.26 ppm. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center-line of the $CDCl_3$ triplet at 77.23 ppm. The abbreviations s, d, t, dd, td, ddd, and m stand for the resonance multiplicities singlet, doublet, triplet, doublet of doublets, triplet of doublets, doublet of doublets of doublets, and multiplet, respectively. Optical rotations were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length; concentrations are reported in g/100 mL. IR spectra were recorded using a Nicolate FTIR instrument. GC (gas chromatography) analysis was performed using a Hewlett Packard HP 6890 Series GC system fitted with a HP-Chiral permethylated β-cyclodextrin column. HPLC (high pressure liquid chromatography) analysis was performed using a Hewlett Packard Series 1100 instrument fitted with a chiral stationary phase (as indicated). SFC (supercritical fluid chromatography) analysis was performed at 40 °C, using a Thar instrument fitted with a chiral stationary phase (as indicated). HRMS (high resolution mass spectrometry) analysis was performed using Waters LCP Premier XE. Glassware for all reactions was oven-dried at 110 ^{o}C and cooled under N_2 atmosphere prior to use. Known compounds **28**, (*S*)-*i*Pr-Quinox, $Pd(PPh_3)_2Cl_2$, **62**, **63**, **71**, and were prepared according to literature procedures.

Synthesis of Substrates

Preparation of 29

To an oven-dried 500 mL round bottom flask equipped with a stir bar were added 23.4 g of **27** (51.0 mmol, 2.30 equiv.) and 200 mL toluene. To this was added a solution

of 5.80 g KO*t*Bu (51.2 mmol, 2.33 equiv.) in 40 mL of THF dropwise via cannulation. The reaction mixture slowly turned a deep red color over 4 h. The mixture was cooled to –78 °C and 2.70 g of salicylaldehyde **28** (22.2 mmol, 1.00 equiv.), dissolved in 20 mL of toluene was added dropwise via cannulation. The mixture was allowed to slowly warm to ambient temperature and stirred 48 hours then quenched with 50 mL of saturated NH_4Cl solution. The mixture was diluted with 100 mL of Et_2O and washed with 100 mL (2 x 50 mL) of water and 60 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 10%-20% EtOAc/hexanes as eluent to give 4.15 g (85% yield, average of two reactions). Isomeric ratio *Z:E* = 10:1, major isomer: R_f = 0.52 with 33% EtOAc/hexanes, colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.02-7.28 (m, 2 H), 6.85-6.95 (m, 2 H), 6.38-6.48 (d, *J* = 11.2 Hz, 2 H), 5.89 (s, 1 H), 5.74-5.86 (m, 1 H), 4.08-4.16 (m, 2 H), 2.37-2.48 (m, 4 H), 1.18-1.29 (m, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 173.3, 153.1, 134.4, 129.9, 128.8, 125.1, 123.8, 120.5, 116.1, 60.9, 33.9, 24.3, 14.3. IR: 3392, 2981, 1705, 1450, 1269, 1195, 1154, 754 cm^{-1}. HRMS $C_{13}H_{16}O_3$ $(M+Na)^+$ calcd. 243.0997, obsvd. 243.0996.

Preparation of 30

To an oven dried 500 mL round bottom flask equipped with a stir bar were added 4.10 g of **29** (18.6 mmol, 1.00 equiv.) in 180 mL THF. To this was slowly added a solution of 3.0 M MeMgBr (130 mmol, 7.00 equiv.) at 0 °C. The reaction mixture was then allowed to warm to rt and was stirred for 12 h. The reaction was quenched by the slow addition of 20 mL of 1 M HCl solution. The mixture was diluted with 50 mL of Et_2O and washed with 100 mL (2 x 50 mL) of water and 60 mL of brine. The organic

extract was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 1:1 EtOAc:hexanes as eluent to give 3.34 g of **30** in 87% yield. Isomeric ratio *Z:E* = 10:1, major isomer: R_f = 0.32 with 33% EtOAc/hexanes, colorless solid. mp = 74-75 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.28-7.07 (m, 2 H), 6.95-6.87 (m, 2 H), 6.40-6.37 (d, *J* = 10.9 Hz), 5.95-5.88 (m, 1 H), 5.34 (s, 1 H), 2.28-2.19 (m, 2 H), 1.67-1.57 (m, 2 H), 1.19 (s, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 152.9, 137.0, 129.8, 128.8, 123.9, 123.4, 120.4, 115.5, 71.3, 43.3, 29.4, 24.1. IR: 3410, 3013, 2971, 1604, 1448, 1377, 1261, 1210, 1147, 1131, 904, 755 cm^{-1}. HRMS $C_{13}H_{18}O_2$ $(M+Na)^+$ calcd. 229.1204, obsvd. 229.1201.

Preparation of 31

To a 100 mL oven dried round bottom flask equipped with a stir bar were added 1.6 g **29** (7.27 mmol, 1 equiv.) followed by 40 mL THF under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C. To this was added 544 mg $LiAlH_4$ portion wise (14.5 mmol, 2 equiv.). The reaction mixture was allowed to slowly warm to rt and stirred overnight. The reaction mixture was cooled to 0 °C, and quenched by the sequential addition of 544 μL of water, 544 μL 15% NaOH, and 1630 μL water. The reaction mixture was warmed to rt, $MgSO_4$ was added, and the mixture was stirred for 15 min and then filtered. The filtrate was concentrated in vacuo and the crude mixture was purified by silica gel column chromatography with 1:3 EtOAc:hexanes to give 777 mg of **53** (60% yield, average of two reactions). Isomeric ratio *Z:E* = 10:1, major isomer: R_f = 0.20 with 33% EtOAc/hexanes, white solid. mp = 45-47 °C. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.06-7.21 (m, 2 H), 6.83-6.94 (m, 2 H), 6.38-6.46 (d, *J* = 11.2 Hz, 1 H), 5.82-5.95 (m, 1

H), 3.59-3.68 (t, J = 6.4Hz, 2 H), 2.17-2.25 (m, 2 H), 1.62-1.74 (m, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 135.9, 130.0, 128.8, 124.1, 120.4, 115.6, 62.7, 32.1, 25.5. IR: 3404, 2938, 2881, 1604, 1448, 1358, 1269, 1225, 1036, 841 cm^{-1}. HRMS $C_{11}H_{14}O_2$ $(M+Na)^+$ calcd. 201.0886, obsvd. 201.0886.

Preparation of 34

To an oven-dried 100 mL Schlenk flask were added 2.10 g of **32** (8.00 mmol, 1 equiv.) and 40 mL of Et_3N. The solution was degassed by 2 cycles of freeze-pump-thaw. To a second oven-dried Schlenk flask was added 1.26 g of **33** (8.96 mmol, 1.12 equiv.), 20 mL of Et_3N and 40 mL of THF. The solution was degassed by 2 cycles of freeze-pump-thaw. To an oven-dried 250 mL round bottom flask equipped with stir bar was added 169 mg of $Pd(PPh_3)_2Cl_2$ (0.240 mmol, 0.0300 equiv.) and 91.4 mg of CuI (0.480 mmol, 0.0600 equiv.). The solutions of **32** and **33** were sequentially transferred via cannula into the flask containing the catalysts. The reaction mixture was then stirred at rt overnight. The reaction mixture was diluted with 50 mL of Et_2O and then 50 mL of 1 M HCl was added and the mixture was allowed to stir for 30 min. The organic layer was washed with 50 mL of 1 M HCl (2 x 25 mL) and 20 mL of brine. The organic extract was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 10% to 20% EtOAc/hexanes as eluent to give 2.03 g of **34** (92.3% yield, average of two reactions). R_f = 0.20 with 20% EtOAc/hexanes, colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.44 (dd, J = 7.6, 1.7 Hz, 1 H), 7.30 (ddd, J = 8.0, 7.6, 1.7 Hz, 1 H), 7.17 (ddd, J = 7.6, 7.6, 1.4 Hz, 1 H), 7.05 (dd, J = 8.1, 1.4 Hz, 1 H), 4.11 (t, J = 6.5 Hz, 2 H), 2.47 (t, J = 6.9 Hz, 2 H), 2.33 (s, 3 H), 2.06 (s, 3 H), 1.84-1.76 (m, 2 H), 1.71-1.63 (m, 2 H). ^{13}C-NMR (75 MHz,

$CDCl_3$) δ = 171.4, 169.1, 151.7, 133.3, 129.0, 126.1, 122.3, 118.0, 94.7, 76.2, 64.1, 28.0, 25.4, 21.2, 21.1, 19.4. IR: 1761, 1733, 1487, 1366, 1237, 1207, 1180, 1037, 907, 755 cm^{-1}. HRMS $C_{16}H_{18}O_4$ $(M+Na)^+$ calcd. 297.1103, obsvd. 297.1097.

Preparation of 35

To an oven dried 50 mL Schlenk flask equipped with a stir bar were added 261 mg of 5% Pd/$BaSO_4$, 150 μL of quinoline (1.27 mmol, 0.42 equiv.) and 5 mL of MeOH. A three-way joint fitted with a balloon of H_2 was attached and the flask. To a separate, oven-dried 50 mL round bottom flask was added 823 mg of **34** (3.00 mmol) and 10 mL MeOH. The solution of **34** is transferred via cannula to the Schlenk flask. An additional 5 mL of MeOH was used for rinsing. The Schlenk flask was evacuated and refilled with H_2 three times. Upon completion as determined by TLC (four days), the reaction mixture was filtered through plug of celite® using 50 mL of MeOH. The filtrate was concentrated in vacuo and dissolved in 100 mL of CH_2Cl_2, washed with 100 mL 0.2 M HCl (2 x 50 mL) and 50 mL brine, dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 1:4 EtOAc:hexanes as eluent to give 576 mg of **35** as a 10:1 mixture of alkene isomers (75% yield, average of 2 reactions). R_f = 0.60 with 2:3 EtOAc:hexanes, colorless oil. Major isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.30-7.15 (m, 3 H), 7.08-6.98 (m, 1 H), 6.30 (d, *J* = 11.5 Hz, 1H), 5.72 (ddd, *J* = 14.7, 11.5, 7.3 Hz, 1 H), 4.03 (t, *J* = 6.6 Hz, 2 H), 2.27 (s, 3 H), 2.21 (ddd, *J* = 14.7, 7.4, 1.7 Hz, 2 H), 2.06 (s, 3 H), 1.68-1.40 (m, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 171.4, 169.4, 148.6, 134.4, 130.6, 130.5, 128.2, 125.9, 123.9, 122.4, 64.5, 28.4, 28.3, 26.2, 21.2, 21.1. IR: 1762, 1733, 1483, 1448, 1367, 1237, 1197,

1170, 1037, 1010, 912, 760 cm^{-1}. HRMS $C_{12}H_{16}O_2$ $(M+Na)^+$ calcd. 299.1254, obsvd. 299.1257.

Preparation of 36

To a 50 mL round bottom flask equipped with stir bar were added 300 mg of **35** (1.09 mmol, 1 equiv.), 300 mg of K_2CO_3 (2.18 mmol, 2.00 equiv.) and 5 mL of MeOH. The reaction mixture was allowed to stir for 10 h. Upon completion by TLC analysis, the reaction mixture was diluted with 20 mL of CH_2Cl_2 and washed with 20 mL of 1 M HCl, 20 mL of water, and 20 mL of brine, dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 2:3 EtOAc:hexanes as eluent to give 188 mg of **36** as a 10:1 mixture of alkene isomers (83% yield, average of two reactions). R_f = 0.45 with 1:1 EtOAc:hexanes, pale yellow oil, major isomer: ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.18-7.08 (m, 2 H), 6.93-6.84 (m, 2 H), 6.41 (d, *J* = 11.3 Hz, 1H), 5.86 (dddd, *J* = 11.3, 7.3, 7.3, 1.1 Hz, 1 H), 5.71 (bs, 1 H), 3.59 (t, *J* = 6.3 Hz, 2 H), 2.15 (ddd, *J* = 14.6, 7.3, 1.6 Hz, 2 H), 1.85 (bs, 1 H), 1.64-1.36 (m, 4 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 153.0, 136.1, 129.9, 128.7, 124.1, 123.8, 120.3, 115.4, 62.8, 32.2, 28.4, 25.7. IR: 3303, 2934, 2859, 1604, 1451, 1228, 1037, 753 cm^{-1}. HRMS $C_{12}H_{16}O_2$ $(M+Na)^+$ calcd. 215.1043, obsvd. 215.1058.

Preparation of 38

To an oven-dried 100 mL round bottom flask were added 2.90 g of **32** (11.1 mmol, 1 equiv.), 10 mL of THF, and 10 mL of Et_3N. The solution was degassed by 2 cycles of freeze-pump-thaw. To a second dried round bottom flask was added 1.24 g of **37** (12.4 mmol, 1.12 equiv.), 10 mL of THF, and 10 mL of Et_3N. The solution was

degassed by 2 cycles of freeze-pump-thaw. To an oven-dried round bottom flask equipped with stir bar was added 233 mg of $Pd(PPh_3)_2Cl_2$ (0.332 mmol, 0.0300 equiv.) and 127 mg of CuI (0.664 mmol, 0.0600 equiv.). Solutions of **32** and **37** were sequentially transferred via cannula into the flask containing the catalysts. The reaction mixture was stirred at rt for 1 h. The reaction mixture was diluted with 50 mL of CH_2Cl_2 and washed with 100 mL (2 x 50 mL) of 1 M HCl, 50 mL of saturated NH_4Cl, and 50 mL of brine. The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 1:2 EtOAc:hexanes to 1:1 EtOAc:hexanes as eluent to give 1.85 g of **72** (71.3% yield, average of two reactions). R_f = 0.20 with 1:1 EtOAc:hexanes, colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.49 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.36 (ddd, *J* = 7.6, 7.6, 1.7 Hz, 1 H), 7.20 (ddd, *J* = 7.6, 7.6, 1.2 Hz, 1 H), 7.09 (dd, *J* = 8.1, 1.2 Hz, 1 H), 4.43 (s, 2 H), 3.78 (bdd, *J* = 9.1, 5.2 Hz, 2 H), 3.70 (m, 2 H), 2.34 (s, 3 H), 2.07 (bs, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 169.2, 151.8, 133.4, 130.0, 126.1, 122.5, 116.8, 90.0, 81.7, 71.3, 62.0, 59.3, 21.1. IR: 3426, 2935, 1760, 1486, 1446, 1368, 1180, 1102, 1010, 908, 756, 733 cm^{-1}. HRMS $C_{13}H_{14}O_4$ $(M+Na)^+$ calcd. 257.0784, obsvd. 257.0789.

Preparation of 39

To an oven-dried 50 mL round bottom flask were added 300 mg of **38** (1.28 mmol, 1 equiv.) and 5 mL THF. The mixture is cooled to 0 °C in an ice bath. In a separate oven-dried round bottom flask 1.6 mL of Red-Al solution (sodium bis(2-methoxyethoxy)aluminum hydride, 65% by weight in toluene, 5.3 mmol, 4.0 equiv.) was diluted with 5 mL of THF. The solution of Red-Al was transferred dropwise via cannula to the reaction mixture. The reaction mixture was stirred at 0 °C for 1 h, and then

warmed to rt. To this was slowly added 20 mL of 0.5 M HCl (gas evolution observed) followed by 20 mL of CH_2Cl_2. The phases were separated, and the aqueous phase was extracted with 80 mL of CH_2Cl_2 (4 x 20 mL). The combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 2% MeOH/CH_2Cl_2 as eluent to give 201 mg of **39** (1:1 mixture of alkene isomers) (81% yield, average of two reactions). R_f = 0.40 with 10% MeOH/CH_2Cl_2, colorless oil. ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.37 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.19 (dddd, *J* = 7.7, 7.4, 1.6, 0.7 Hz, 1 H), 7.13 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1 H), 7.05 (ddd, *J* = 8.0, 1.9, 0.7 Hz, 1 H), 6.93-6.85 (m, 4 H), 6.78 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.65 (d, *J* = 11.4 Hz, 1 H), 6.30 (dt, *J* = 16.1, 6.0 Hz, 1 H), 6.07 (dt, *J* = 11.4, 7.1 Hz, 1 H), 5.99 (bs, 1 H), 5.61 (bs, 1 H), 4.22 (dd, *J* = 6.0, 1.4 Hz, 2 H), 4.07 (dd, *J* = 7.1, 1.1 Hz, 2 H), 3.82-3.71 (m, 4 H), 3.64 (ddd, *J* = 4.3, 4.3, 1.5 Hz, 2 H), 3.57 (ddd, *J* = 3.4, 2.1, 1.5 Hz, 2 H), 2.38-2.26 (m, 2 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 153.4, 153.1, 130.2, 130.0, 129.4, 129.0, 128.7, 127.8, 127.7, 127.1, 124.0, 123.0, 120.9, 120.6, 116.2, 116.2, 72.2, 72.1, 71.5, 67.7, 62.1, 61.9. IR: 3301, 2932, 2867, 1656, 1603, 1455, 1357, 1251, 1093, 1054, 976, 753 cm^{-1}. HRMS $C_{11}H_{14}O_3$ $(M+Na)^+$ calcd. 217.0835, obsvd. 217.0845.

Optimization of Reaction Conditions

General Procedure for Optimization

For optimization, four reactions were run simultaneously in separate 5/10 mL side-arm flasks attached to a four-neck cow fitted with a three way adaptor with a balloon of O_2 attached. A standard solution was prepared by the addition of 412.6 mg of the substrate **30** and 63.3 mg of the internal standard 2-methoxynaphthalene to a 2 mL

volumetric flask, followed by the addition of MeOH. The flask was briefly sonicated to dissolve **30** and stirred to give a solution with [**30**] = 1.00 M and [2-methoxynaphthalene] = 0.20 M.

Each optimization reaction was performed as described in the following example: To a 5 mL side-arm round bottom flask equipped with a stir bar was added 2.6 mg $Pd(MeCN)_2Cl_2$ (0.010 mmol, 0.10 equiv.), 2.7 mg of $CuCl_2$ (0.020 mmol, 0.20 equiv.), 7.7 mg (*S*)-*i*Pr-quinox (0.032 mmol, 0.32 eqiuv), 4.0 mg of $KHCO_3$ (0.040 mmol, 0.40 equiv.), and 900 μL of MeOH, and the flask was attached to a four-neck cow (Note: for reactions using co-solvents, 800 μL of solvent and 100 μL MeOH were added). A three-way joint fitted with a balloon of O_2 was attached, and the apparatus was evacuated (using house vacuum) and refilled with oxygen three times. The mixture was stirred vigorously for 20 min at rt. A 100 μL portion of the standard solution of **30** (0.100 mmol, 1 equiv.) and 2-methoxy naphthalene (0.020 mmol, 0.20 equiv.) was added dropwise to the reaction mixture. Aliquots (ca. 50 μL) of the reaction were taken periodically via syringe. Reaction samples were passed through a short silica plug eluting with 2 mL of EtOAc and analyzed by GC and referenced against a time zero sample containing the standard solution of **30** and 2-methoxynaphthalene diluted in EtOAc. GC yields were calculated based on the ratio of product to internal standard corrected for the response factor. Enantiomeric and diastereomeric ratios were determined using GC with a column equipped with a chiral stationary phase (see Table 2.8 for separation conditions).

For optimization of the reaction conditions for H_2O, NaN_3 and EG, the same procedure as the general procedure was followed, except reactions were run at 0.2 mmol scale and products were isolated to determined isolated yield and stereoselectivity.

Preparation of 41

To a 100 mL Schlenk flask equipped with a stir bar were added 5.2 mg $Pd(MeCN)_2Cl_2$ (0.020 mmol, 0.040 equiv.), 4.0 mg of CuCl (0.040 mmol, 0.080 equiv.), 16.8 mg of (*S*)-*i*Pr-quinox (0.700 mmol, 0.140 equiv.), 20.0 mg of $KHCO_3$ (0.200 mmol, 0.400 equiv.), 1 mL of MeOH (25 mmol, 50 equiv.), 2 mL of THF, and 2 mL toluene. A three-way joint fitted with a balloon of O_2 was attached and flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at rt under an atmosphere of O_2. To the reaction mixture, 103 mg of **30** (0.500 mmol, 1 equiv.) was added. The reaction mixture was stirred for 3 h and diluted with 10 mL of EtOAc. The reaction mixture was then washed with 10 mL 1 M NH_4Cl, 10 mL brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 2% to 10% EtOAc/hexanes as eluent to give 85.7 mg of product (72% yield, average of two reactions). Diastereomeric ratio: 10:1. R_f = 0.70 with 33% EtOAc/hexanes, white solid. mp = 81-84 °C. $[\alpha]^{20}_D$ = –31.5 (c = 3.53, $CHCl_3$). Major diastereomer: ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.12 (s, 1 H), 7.20 (ddd, *J* = 8.9, 7.2, 1.6, 1 H), 7.09 (dd, *J* = 7.6, 1.8 Hz, 1 H), 6.91-6.82 (m, 2 H), 4.42-4.32 (m, 2 H), 3.36 (s, 3 H), 1.83 (ddd, *J* = 14.4 Hz, *J* = 7.0 Hz, *J* = 1.4 Hz, 2 H), 1.72-1.49 (m, 2 H), 1.24 (s, 3 H), 1.22 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.8, 129.5, 129.3, 123.5, 119.9, 117.7, 85.5, 82.8, 81.1, 57.9, 38.3, 28.3, 28.2, 27.9, 27.7. IR: 3285, 2869, 2930,

1487, 1456, 1367, 1236, 1102, 1056, 754 cm^{-1}. HRMS $C_{14}H_{20}O_3$ $(M+Na)^+$ calcd. 259.1310, obsvd. 259.1308.

Preparation of 42

To a 100 mL side-arm round bottom flask equipped with a stir bar were added 5.2 mg $Pd(MeCN)_2Cl_2$ (0.020 mmol, 0.040 equiv.), 4.0 mg of CuCl (0.040 mmol, 0.080 equiv.), 16.8 mg of (*S*)-*i*Pr-quinox (0.700 mmol, 0.140 equiv.), 20 mg of $KHCO_3$ (0.20 mmol, 0.40 equiv.) and 2.6 mL of toluene. A three-way joint fitted with a balloon of O_2 was attached and flask was evacuated and refilled three times with O_2. The mixture was stirred for 20 min at rt. To the reaction mixture, a 2.3 mL of *n*-butanol (25 mmol, 50 equiv.) and 103 mg of **30** (0.500 mmol, 1.00 equiv.) were added. The reaction mixture was stirred for 12 h and diluted with 10 mL of EtOAc. The reaction mixture was then washed with 1 M NH_4Cl (10 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography with 10% EtOAc/hexanes as eluent to give 87.5 mg of product (63% yield, average of two reactions*)*. Diastereomeric ratio: 5:1, major diastereomer: R_f = 0.75 with 33% EtOAc/hexanes, colorless liquid. $[\alpha]^{20}_D$ = –8.2 (c = 1.0, $CHCl_3$), ^{1}H-NMR (500 MHz $CDCl_3$) δ = 8.31 (s, 1 H), 7.22 (dd, *J* = 1.6, 8.7 Hz, 1 H), 7.09 (dd, *J* = 1.6, 7.5 Hz, 1 H), 6.91-6.83 (m, 2 H), 4.43 (d, *J* = 4.1 Hz, 1 H), 4.3 (ddd, *J* = 7.1, 4.2 Hz, 1 H), 3.47 (ddd, *J* = 9.3, 6.7, 1.0 Hz, 1 H), 3.37 (ddd, *J* = 9.3, 6.5, 1.0 Hz, 1 H), 2.02-1.82 (m, 2 H), 1.70-1.29 (m, 6 H), 1.24 (s, 3 H), 1,21 (s, 3 H), 0.90 (t, *J* = 7.14 Hz, 3 H). ^{13}C-NMR (100 MHz $CDCl_3$) δ = 155.9, 129.2, 124.4, 119.7, 117.7, 83.3, 82.8, 81.7, 70.0, 38.4, 31.9, 28.1, 28.0, 27.9, 19.5, 14.0. IR: 3289, 2962, 2931,

1455, 1367, 1237, 1095 cm^{-1}. HRMS $C_{17}H_{26}O_3$ $(M+Na)^+$ calcd. 301.1780, obsvd. 301.1777.

Preparation of 43

The procedure described for **42** was followed except 2.9 mL toluene and 2.1 mL of 3-butene-1-ol (25 mmol, 50 equiv.) were used. 78.6 mg (57% yield, average of two reactions. Diastereomeric ratio: 4:1, major diastereomer: R_f = 0.75 with 33% EtOAc/hexanes, colorless liquid, $[\alpha]^{20}_D$ = +11.0 (c = 0.1, $CHCl_3$), ^{1}H-NMR (500 MHz $CDCl_3$) δ = 8.28 (s, 1 H), 7.20 (td, *J* = 1.8, 7.7 Hz, 1 H), 7.04 (dd, *J* = 1.5, 7.7 Hz, 1 H), 6.90-6.83 (m, 2 H), 5.82 (ddd, *J* = 6.5, 3.3, 7.0 Hz, 1 H), 5.02-4.98 (m, 2 H), 4.44 (d, *J* =3.9, 1 H), 4.38 (ddd, *J* = 6.9, 4.1 Hz, 1 H), 3.52 (ddd, *J* = 9.2, 6.8 Hz, 1 H), 3.42 (ddd, *J* = 9.3, 6.6 Hz, 1 H), 2.38 (dd, *J* = 6.2, 8.2 Hz, 1 H), 2.09-1.82 (m, 2 H), 1.71-1.4 (m, 2 H), 1.23 (s, 3 H), 1.21 (s, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 155.8, 135.2, 129.3, 129.3, 124.3, 119.7, 117.7, 116.8, 83.3, 82.9, 81.7, 69.3, 38.3, 34.4, 28.1, 28.0, 27.9. IR: 3284, 2971, 1733, 1652, 1558, 1487, 1054 cm^{-1}. HRMS $C_{17}H_{24}O_3$ $(M+Na)^+$ calcd. 299.1623, obsvd. 299.1615.

Preparation of 44

The procedure described for **42** was followed except 1.5 mL of THF, 1.5 mL toluene, and 2.0 mL of 2-methoxyethanol (25 mmol, 50 equiv.) were used. 74.2 mg (53% yield, average of two reactions. Diastereomeric ratio: 9:1, major diastereomer: R_f = 0.35 with 33% EtOAc/hexanes, colorless oil, $[\alpha]^{20}_D$ = –35.0 (c = 0.15, $CHCl_3$), ^{1}H-NMR (400 MHz $CDCl_3$) δ = 8.20 (s, 1 H), 7.20 (dd, *J* = 1.8, 6.9 Hz, 1 H), 7.11 (dd, *J* = 7.7 Hz, 1 H), 6.91-6.85 (m, 2 H), 4.54 (d, *J* = 4.4 Hz, 1 H), 4,43 (ddd, *J* = 7.0, 4.3, 4.3 Hz, 1 H), 3.65-3.51 (m, 4 H), 3.33 (s, 3 H), 2.00-1.83 (m, 2 H), 1.74-1.61 (m, 1 H), 1.56-1.49 (m, 1

H), 1.24 (s, 3 H), 1.20 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.9, 129.5, 129.4, 124.3, 119.9, 118.0, 83.3, 82.9, 81.7, 72.1, 69.1, 59.2, 38.4, 28.1, 28.0, 28.0. IR: 3266, 2968, 2872, 1486, 1097, 753 cm^{-1}. HRMS $C_{16}H_{24}O_4$ $(M+Na)^+$ calcd. 303.1572, obsvd. 303.1566.

Preparation of 45

The procedure described for **42** was followed except 3.3 mL toluene and 1.7 mL of 2-chloroethanol (25 mmol, 50 equiv.) were used. 86.6 mg (61% yield, average of two reactions. Diastereomeric ratio: 5:1, major diastereomer: $[\alpha]^{20}_D = -38.0$ (c = 0.6, $CHCl_3$) R_f = 0.50 with 20% EtOAc/hexanes, colorless oil, ^{1}H-NMR (400 MHz $CDCl_3$) δ = 8.29 (s, 1 H), 7.22 (ddd, *J* = 7.5, 0.9 Hz, 1 H), 7.13-7.09 (m, 1 H), 6.93-6.85 (m, 2 H), 4.50 (d, *J* = 3.4 Hz, 1 H), 4.43 (td, *J* = 7.0, 3.5 Hz, 1 H), 3.76-3.55 (m, 4 H), 3.33 (s, 3 H), 2.01 (m, 2 H), 1.74-1.58 (m, 2 H), 1.26 (s, 3 H), 1.24 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.7, 129.8, 129.4, 124.2, 120.0, 118.1, 83.4, 81.9, 69.7, 43.3, 38.3, 28.1, 27.9, 27.8. IR: 3265, 2966, 1490, 1461, 1364, 1190, 1104, 1049, 754 cm^{-1}. HRMS $C_{15}H_{21}ClO_3$ $(M+Na)^+$ calcd. 307.1077, obsvd. 307.1079.

Preparation of 46

The procedure described for **42** was followed except 0.7 mL of THF and 0.7 mL toluene (1:1) and 1.6 mL of benzylalcohol (15 mmol, 50 equiv.) were used. 47.7 mg (51% yield, average of two reactions. Diastereomeric ratio: 6:1, major diastereomer: R_f = 0.50 with 20% EtOAc/hexanes, colorless liquid, $[\alpha]^{20}_D = -49.5$ (c = 0.39, $CHCl_3$),^{1}H-NMR (300 MHz $CDCl_3$) δ = 8.33 (s, 1 H), 7.36-7.29 (m, 5 H), 7.22 (td, *J* = 7.7, 1.4 Hz, 1 H), 7.11 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.94 (dd, *J* = 8.0, 1.0 Hz, 1 H), 6.88 (td, *J* = 7.4, 1.1 Hz, 1 H), 4.64 (d, *J* = 12.0 Hz, 1 H), 4.54 (d, *J* = 3.9 Hz, 1 H), 4.43 (td, *J* = 7.0, 3.9 Hz, 1

H), 4.34 (d, *J* = 12.0 Hz, 1 H), 1.99-1.88 (m, 2 H), 1.66 (dt, *J* = 12.0, 7.3 Hz, 1 H), 1.59-1.51 (m, 1 H), 1.22 (s, 3 H), 1.20 (s, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 155.9, 137.9, 129.5, 129.4, 128.5, 128.1, 127.9, 124.0, 119.9, 118.0, 83.0, 81.7, 81.6, 71.2, 38.3, 28.0, 27.9, 27.8. IR: 3285, 2970, 2870, 1717, 1615, 1506, 1455, 1180, 1097, 1027, 756 cm^{-1}. HRMS $C_{20}H_{24}O_3$ $(M+Na)^+$ calcd. 335.1623, obsvd. 335.3925.

Preparation of 47

The procedure described for **42** was followed except 1.9 mL toluene and 1.1 mL of 2-(trimethylsilyl)ethanol (7.5 mmol, 25 equiv.) were used. 62.1 mg (64% yield, average of two reactions). Diastereomeric ratio: 5:1, major diastereomer: R_f = 0.85 with 20% EtOAc/hexanes, colorless liquid, $[\alpha]^{20}_D$ = –21 (c = 0.25, $CHCl_3$),^{1}H-NMR (300 MHz $CDCl_3$) δ = 8.31 (s, 1 H), 7.18 (td, *J* = 7.7, 1.1 Hz, 1 H), 7.10 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.89-6.84 (m, 2 H), 4.50 (d, *J* = 4.5 Hz, 1 H), 4.37 (td, *J* = 7.1, 4.6 Hz, 1 H), 3.63-3.57 (m, 1 H), 3.50-3.45 (m, 1 H), 1.91-1.80 (m, 2 H), 1.63 (dt, *J* = 12.1, 7.5 Hz, 1 H), 1.46 (ddd, *J* = 12.1, 8.2, 6.3 Hz, 1 H), 1.21 (s, 3 H) 1.16 (s, 3 H), 1.04 (m, 1 H), 0.92 (m, 1 H), -0.02 (s, 9 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 155.9, 129.1, 129.0, 124.3, 119.7, 117.6, 82.6, 82.2, 81.5, 67.6, 38.3, 28.1, 27.8, 27.7, 18.5, 1.2. IR: 3304, 2966, 2894, 1586, 1486, 1384, 1248, 1096, 859, 836, 755 cm^{-1}. HRMS $C_{18}H_{30}O_3Si$ $(M+Na)^+$ calcd. 345.1862, obsvd. 345.1861.

Preparation of 48

The procedure described for **42** was followed except 3.0 mL toluene and 2.0 mL of (–)-myrtenol (12.5 mmol, 25 equiv.) were used. 97.9 mg (55% yield, average of two reactions). Diastereomeric ratio: 9:1, major diastereomer: $[\alpha]^{20}_D$ = –31.3 (c = 0.7, $CHCl_3$) R_f = 0.76 with 33% EtOAc/hexanes, colorless liquid. ^{1}H-NMR (400 MHz $CDCl_3$) δ =

8.28 (s, 1 H), 7.20-7.16 (m, 1 H), 7.08 (dd, *J* = 7.5, 1.4 Hz, 1 H), 6.89-6.83 (m, 2 H), 5.46 (dt, *J* = 2.9, 1.4 Hz, 1 H) 4.51 (d, *J* = 3.9 Hz, 1 H), 4.38 (td, *J* = 5.4, 3.2 Hz, 1 H), 3.90 (dd, *J* = 12.3, 1.7 Hz, 1H), 3.75-3.72 (m, 1 H), 2.33 (dt, *J* = 8.6, 5.6 Hz, 1 H), 2.24 (m, 2 H), 2.12 (t, *J* = 5.6 Hz, 1 H), 2.01 (m, 1 H), 1.94-1.88 (m, 2 H), 1.66-1.61 (m, 1 H) 1.54-1.50 (m, 1 H), 1.27 (s, 3 H), 1.21 (s, 3 H), 1.19 (s, 3 H) 1.07 (d, *J* = 8.6 Hz, 1 H), 0.86 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.7, 144.9, 129.1, 129.2, 129.0, 124.1, 120.1, 119.5, 117.5, 82.6, 81.6, 81.5, 81.5, 76.7, 72.4, 43.4, 41.0, 40.8, 38.1, 37.9, 31.5, 31.3, 31.2, 28.0, 27.7, 27.6, 26.2, 21.1, 20.9. IR: 3303, 2969, 2914, 1615, 1486, 1381, 1282, 1126, 1035, 887, 753 cm^{-1}. HRMS $C_{23}H_{32}O_3$ $(M+Na)^+$ calcd. 379.2249, obsvd. 379.2254.

Preparation of 49

To a 100 mL side-arm round bottom flask equipped with a stir bar were added 8.3 mg Pd[(*S*)-*i*Pr-quinox]Cl_2 (0.020 mmol, 0.040 equiv.), 15.0 mg of Cu[(*S*)-*i*Pr-quinox]Cl_2 (0.0400 mmol, 0.0800 equiv.), 1.2 mg of (*S*)-*i*Pr-quinox (0.0050 mmol, 0.010 equiv.), 4.4 mg of $NaHCO_3$ (0.050 mmol, 0.10 equiv.) and 4.5 mL *t*AmylOH. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled three times with O_2. The mixture was stirred for 20 min at rt. To the reaction mixture, a 450 μL of water (25 mmol, 50 equiv.) and 103 mg of **30** (0.500 mmol, 1 equiv.) were added. The reaction mixture was stirred for 24 h and diluted with 10 mL of EtOAc. The reaction mixture was then washed with 1 M NH_4Cl (10 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography with EtOAc/hexanes (4% to 10%) as eluent to give 69.9 mg of product (63% yield, average of two reactions).

Diastereomeric ratio: 5:1, major diastereomer: R_f = 0.60 with 33% EtOAc/hexanes, white solid. $[\alpha]^{20}_D$ = –17.0 (c = 0.1, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 8.40 (s, 1 H), 7.20 (ddd, *J* = 8.1, 7.4, 1.7 Hz, 1 H), 7.04 (dd, *J* = 7.6, 1.7 Hz, 1 H), 6.89 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.84 (td, *J* = 7.4, 1.2 Hz, 1 H), 4.58 (d, *J* = 6.8 Hz, 1 H), 4.27 (apparent q, *J* = 6.8 Hz, 1 H), 3.31 (bs, 1 H), 1.95-1.83 (m, 2 H), 1.81-1.75 (m, 2 H), 1.33 (s, 3 H), 1.27 (s, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 156.1, 129.7, 128.8, 124.4, 119.9, 118.0, 83.3, 81.1, 78.9, 38.5, 29.1, 28.3, 28.2. IR: 3297, 2968, 1237, 752 cm^{-1}. HRMS $C_{13}H_{18}O_3$ $(M+Na)^+$ calcd. 245.1154, obsvd. 245.1146.

Preaparation of 50

The procedure described for **49** was followed except 3.6 mL *t*AmylOH and 1.4 mL of ethylene glycol (25 mmol, 50 equiv.) were used. 78.5 mg (59% yield, average of two reactions). Diastereomeric ratio: 10:1, major diastereomer: R_f = 0.30 with 66% EtOAc/hexanes, colorless liquid. $[\alpha]^{20}_D$ = –100 (c = 0.1, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.27 (s, 1 H), 7.21 (td, *J* = 7.7, 1.2 Hz, 1 H), 7.07 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.91 (dd, *J* = 8.1, 0.9 Hz, 1 H), 6.87 (td, *J* = 7.4, 1.1 Hz, 1 H), 4.44-4.38 (m, 2 H), 3.81-3.64 (m, 3 H), 3.58 (ddd, *J* = 10.7, 5.9, 3.0 Hz, 1 H), 2.89 (bs, 1 H), 1.93-1.87 (m, 2 H), 1.75-1.65 (m, 2 H), 1.29 (s, 3 H), 1.27 (s, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.9, 129.8, 129.3, 124.1, 118.1, 85.1, 83.1, 81.7, 71.5, 61.9, 38.5, 28.5, 28.3, 28.0. IR: 3263, 2967, 2869, 1454, 1041, 754 cm^{-1}. HRMS $C_{15}H_{22}O_4$ $(M+Na)^+$ calcd. 289.1416, obsvd. 289.1417.

Preparation of 51

To a 100 mL side-arm round bottom flask equipped with a stir bar was added 8.3 mg Pd[(*S*)-*i*Pr-quinox]Cl_2 (0.020 mmol, 0.040 equiv.), 15.0 mg of Cu[(*S*)-*i*Pr-quinox]Cl_2

(0.0400 mmol, 0.0800 equiv.), 1.2 mg of (*S*)-*i*Pr-quinox (0.0050 mmol, 0.010 equiv.), 4.4 mg of $NaHCO_3$ (0.050 mmol, 0.10 equiv.) and 5.0 mL *t*AmylOH. A three-way joint fitted with a balloon of O_2 was attached and flask was emptied and refilled three times with O_2. The mixture was stirred for 20 min at rt. To the reaction mixture, 65 mg of NaN_3 (1.0 mmol, 2.0 equiv.) and 103 mg of **30** (0.200 mmol, 1 equiv.) were added. The reaction mixture was stirred for 48 h at 30 °C and diluted with 10 mL of EtOAc. The reaction mixture was then washed with 1.0 M NH_4Cl (10 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was purified with flash silica-gel column chromatography with 2% to 10% EtOAc/hexanes as eluent to give 62.9 mg of product (50% yield, average of two reactions). $[\alpha]^{20}_D = +22.1$ (c = 0.25, $CHCl_3$). ^{1}H-NMR for major diastereomer (400 MHz $CDCl_3$) δ = 8.21 (s, 1 H), 7.28-7.23 (m, 1H), 7.18-7.15 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.01-6.88 (m, 2 H), 4.70-4.65 (d, *J* = 3.2 Hz, 1 H), 4.35-4.25 (td, *J* = 3.2, 6.7 Hz, 1 H), 1.9-1.8 (m, 2 H), 1.78-1.62 (m, 2 H), 1.23 (s, 6 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 155.3, 130.3, 129.9, 123.3, 120.4, 118.8, 84.3, 81.5, 66.9, 38.1, 28.4, 28.0, 27.8. IR: 3264, 2971, 2100, 1456, 1251, 754 cm^{-1}. HRMS $C_{13}H_{17}N_3O_2$ $(M+Na)^+$ calcd. 270.1216, obsvd. 270.1214.

^{1}H-NMR for minor diastereomer (400 MHz $CDCl_3$) δ = 8.34 (s, 1 H), 7.28-7.23 (m, 1 H), 7.18-7.15 (dd, *J* = 1.5, 7.5 Hz, 1 H), 7.01-6.88 (m, 2 H), 4.78-4.75 (d, *J* = 3.2, 1 H), 4.44-4.38 (td, *J* = 3.2, 6.7 Hz, 1 H), 2.1-1.9 (m, 2 H), 1.78-1.62 (m, 2 H), 1.31 (s, 3 H), 1.27 (s, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$) δ = 155.4, 130.6, 130.5, 120.2, 118.8, 83.9, 81.6, 68.5, 38.1, 28.8, 28.0, 27.8. IR: 3264, 2971, 2100, 1456, 1251, 754 cm^{-1}.

Preparation of 53 (DA)

To a 250 mL side-arm round bottom flask equipped with a stir bar were added 5.2 mg $Pd(MeCN)_2Cl_2$ (0.020 mmol, 0.040 equiv.), 4.0 mg of CuCl (0.040 mmol, 0.080 equiv.), 16.8 mg of (*S*)-*i*Pr-Quinox (0.070 mmol, 0.140 equiv.), 20.0 mg of $KHCO_3$ (0.200 mmol, 0.40 equiv.), and 2.2 mL toluene. A three-way joint fitted with a balloon of O_2 was attached, and flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 minutes at room temperature under an atmosphere of O_2. To the reaction mixture, 103.1 mg of **30** (0.5000 mmol, 1 equiv.) as a solution in 2.8 mL of ethyl propenyl ether (25 mmol, 50 equiv., *Z*:*E* = 10:1) was added (*Note*: ethyl propenyl ether was purchased as a 3:1 mixture of isomers and enriched through multiple fractional distillations). The reaction flask was evacuated and refilled with O_2 twice more. The reaction mixture was stirred for 24 h and passed through a plug of silica with 50 mL EtOAc and concentrated in vacuo, and then purified with flash alumina column chromatography with hexanes followed by 1% EtOAc/hexanes to 2% EtOAc/hexanes as eluent to give 104.1 mg of the product (72% yield). Diastereomeric ratio: 33:5:1, major diastereomer: R_f = 0.60 w/ 1:4 EtOAc:hexanes, clear oil. $[\alpha]^{20}_D$ = –30.8° (c = 1.73, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31-7.28 (m, 1 H), 7.13 (ddd, *J* = 7.7 Hz, *J* = 7.7 Hz, *J* = 1.7 Hz, 1 H), 6.87-6.81 (m, 2 H), 5.04 (d, *J* = 2.6 Hz, 1 H), 4.34 (ddd, *J* = 6.8 Hz, *J* = 6.8 Hz, *J* = 4.6 Hz, 1 H), 3.98 (dq, *J* = 9.5 Hz, *J* = 7.1 Hz, 1 H), 3.60 (dq, *J* = 9.5 Hz, *J* = 7.1 Hz, 1 H), 3.09 (dd, *J* = 5.0 Hz, *J* = 5.0 Hz, 1 H), 2.42 (qdd, *J* = 7.1 Hz, *J* = 5.5 Hz, *J* = 2.5 Hz, 1 H), 2.18-2.07 (m, 1 H), 1.71-1.50 (m, 3 H), 1.31 (s, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H), 1.20 (s, 3 H), 1.07 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ 153.2, 129.4, 127.8, 123.1, 120.3, 116.6, 101.6, 79.7, 77.8, 64.6, 43.4, 39.0, 33.8, 30.7,

29.0, 27.3, 15.3, 10.6, IR 2969, 2879, 1581, 1487, 1454, 1376, 1365, 1222, 1149, 1093, 1040, 978, 932, 752 cm^{-1}. HRMS $C_{18}H_{26}O_3$ $(M+Na)^+$ calcd. 313.1780, obsvd. 313.1775. Relative stereochemistry assigned by a combination of coupling constants, as compared to reported Diels Alder adducts with ethyl propenyl ether and a related quinone methide, and X-ray crystal structure analysis of the lactone derivative.

Preparation of 54

To a 250 mL side-arm round bottom flask equipped with a stir bar were added 5.2 mg $Pd(MeCN)_2Cl_2$ (0.020 mmol, 0.040 equiv.), 4.0 mg of CuCl (0.040 mmol, 0.080 equiv.), 16.8 mg of (*S*)-*i*Pr-Quinox (0.070 mmol, 0.140 equiv.), 20.0 mg of $KHCO_3$ (0.200 mmol, 0.40 equiv.), and 2.2 mL toluene. A three-way joint fitted with a balloon of O_2 was attached, and flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 89.1 mg of **31** (0.5000 mmol, 1 equiv.) as a solution in 2.8 mL of ethyl propenyl ether (25 mmol, 50 equiv., *Z*:*E* = 10:1) was added (*Note*: ethyl propenyl ether was purchased as a 3:1 mixture of isomers and enriched through multiple fractional distillations). The reaction flask was evacuated and refilled with O_2 twice more. The reaction mixture was stirred for 24 h and passed through a plug of silica with 50 mL EtOAc and concentrated in vacuo, and then purified with flash alumina column chromatography with 1% EtOAc/hexanes to 2% EtOAc/hexanes as eluent to give 88.2 mg of the product (67% yield). Diastereomeric ratio: 33:8:1, major diastereomer: R_f = 0.70 w/ 1:3 EtOAc:hexanes, clear oil. $[\alpha]^{20}_D = -36.1°$ (c = 0.58, $CHCl_3$), ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.26-7.22 (m, 1 H), 7.13 (ddd, *J* = 7.7 Hz, *J* = 7.7 Hz, *J* = 1.7 Hz, 1 H), 6.88-6.81 (m, 2 H), 5.07 (d, *J* = 2.5 Hz, 1 H), 4.22 (ddd, *J* = 7.1 Hz, *J* = 7.1 Hz, *J* = 5.5

Hz, 1 H), 3.98 (dq, *J* = 9.6 Hz, *J* = 7.1 Hz, 1 H), 3.90 (ddd, *J* = 7.3 Hz, *J* = 5.3 Hz, *J* = 5.3 Hz, 1 H), 3.65 (dd, *J* = 7.3 Hz, *J* = 7.1 Hz, 1 H), 3.61 (dq, *J* = 9.6 Hz, *J* = 7.1 Hz, 1 H), 3.15 (dd, *J* = 5.3 Hz, *J* = 5.3 Hz, 1 H), 2.43 (qdd, *J* = 7.0 Hz, *J* = 5.5 Hz, *J* = 2.5 Hz, 1 H), 2.13-2.03 (m, 1 H), 1.94-1.71 (m, 2 H), 1.65-1.53 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 1.06 (d, *J* = 7.0 Hz, 3 H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ 153.3, 129.1, 127.9, 122.7, 120.5, 116.7, 101.7, 79.1, 67.4, 64.7, 43.4, 33.7, 30.4, 26.7, 15.3, 10.1, IR 2977, 2875, 1581, 1487, 1454, 1375, 1352, 1237, 1222, 1159, 1064, 1041, 981, 931, 754 cm^{-1}. HRMS $C_{16}H_{22}O_3$ $(M+Na)^+$ calcd. 285.1467, obsvd. 285.1472.

Preparation of 55

The procedure described for **54** was followed except 89.0 mg of **31** (0.500 mmol, 1 equiv.) was added**.** Reaction was stirred for 7 h. Yield = 68%, average of two reactions. Diastereomeric ratio: 10:1, major diastereomer: R_f = 0.40 with 33% EtOAc/hexanes, white solid. mp = 64-65 °C. $[\alpha]^{20}_D$ = –62.0 (c = 0.1, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.09 (s, 1 H), 7.22 (dd, *J* = 1.6, 8.3 Hz, 1 H), 7.09 (dd, *J* = 7.5, 1.9 Hz, 1 H), 6.94-6.84 (m, 2 H), 4.39-4.20 (m, 2 H), 3.98-3.78 (m, 2 H), 3.39 (s, 3 H), 1.89-1.65 (m, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 155.9, 129.7, 129.4, 123.0, 119.9, 117.6, 86.2, 81.5, 69.2, 57.9, 28.2, 26.0. IR: 3282, 2933, 2874, 1486, 1456, 1149, 1057, 753 cm^{-1}. HRMS $C_{12}H_{16}O_3$ $(M+Na)^+$ calcd. 231.0997, obsvd. 231.0990.

Preparation of 56

To a 100 mL side-arm round bottom flask equipped with a stir bar were added 5.2 mg $Pd(MeCN)_2Cl_2$ (0.020 mmol, 0.040 equiv.), 4.0 mg of CuCl (0.040 mmol, 0.080 equiv.), 16.8 mg of (*S*)-*i*Pr-quinox (0.0700 mmol, 0.140 equiv.), 20.0 mg of $KHCO_3$ (0.200 mmol, 0.400 equiv.), 1 mL of MeOH (25 mmol, 50 equiv.), 1 mL of THF, and 2

mL toluene. A three-way joint fitted with a balloon of O_2 was attached, and flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at rt under an atmosphere of O_2. To the reaction mixture, 96.1 mg of **36** (0.500 mmol, 1 equiv.) in a solution in 1 mL THF were added. The reaction mixture was stirred for 24 h and diluted with 10 mL of EtOAc. The reaction mixture was then washed with 1 M NH_4Cl (10 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography with 2% to 10% EtOAc/hexanes as eluent to give 55.0 mg of product (50% yield, average of two reactions). Diastereomeric ratio: 6:1, major diastereomer: R_f = 0.66 with 1:1 EtOAc:hexanes, white solid. mp = 98-103 °C. $[\alpha]^{20}_D$ = –14.0 (c = 0.28, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.97 (s, 1 H), 7.22 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1 H), 7.03 (dd, *J* = 7.5, 1.7 Hz, 1 H), 6.91-6.83 (m, 2 H), 4.23 (d, *J* = 5.6 Hz, 1 H), 4.16-4.05 (m, 1 H), 3.75-3.68 (m, 1 H), 3.49 (ddd, *J* = 11.5, 11.5, 2.7 Hz, 1 H), 3.38 (s, 3H), 1.85-1.75 (m, 1 H), 1.65-1.15 (m, 5 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 155.8, 129.9, 129.7, 122.9, 119.9, 117.6, 87.3, 80.0, 69.1, 57.9, 28.1, 25.9, 23.1. IR: 3326, 2937, 2855, 1506, 1457, 1241, 1082, 756 cm^{-1}. HRMS $C_{13}H_{18}O_3$ $(M+Na)^+$ calcd. 245.1148, obsvd. 245.1152.

Preparation of 57

To a 200 mL side-arm round bottom flask equipped with a stir bar were added 5.2 mg $Pd(MeCN)_2Cl_2$ (0.020 mmol, 0.040 equiv.), 4.0 mg of CuCl (0.040 mmol, 0.080 equiv.), 16.8 mg of (*S*)-*i*Pr-quinox (0.0700 mmol, 0.140 equiv.), 42.0 mg of $NaHCO_3$ (0.500 mmol, 1.00 equiv.), 1.0 mL of MeOH (25 mmol, 50 equiv.), 1 mL of THF, and 2 mL toluene. A three-way joint fitted with a balloon of O_2 was attached, and flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at rt. To

the reaction mixture, 97.1 mg of **37** (0.500 mmol, 1 equiv.) in a solution in 1 mL THF were added. The reaction mixture was stirred for 24 h and diluted with 10 mL of CH_2Cl_2. The reaction mixture was then washed with 1 M NH_4Cl (10 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was passed through a plug of alumina with 200 mL of 1:1 EtOAc:hexanes followed by 10% MeOH/EtOAc (to separate the product from ligand, which are inseparable by silica chromatography). The portion eluted with 10% MeOH/EtOAc was concentrated in vacuo, then purified with flash silica-gel column chromatography with 1% MeOH/CH_2Cl_2 as eluent to give 39.5 mg of the product (30% yield, average of two reactions). Diastereomeric ratio: 6:1, major diastereomer: R_f = 0.60 with 10% MeOH/CH_2Cl_2, clear oil. $[\alpha]^{20}_D = -26.3$ (c = 1.88, $CHCl_3$). ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.64 (s, 1 H), 7.23 (dd, *J* = 8.5, 1.5 Hz, 1 H), 6.98 (dd, *J* = 7.6, 1.8 Hz, 1 H), 6.93-6.83 (m, 2 H), 4.27 (d, *J* = 6.0 Hz, 1 H), 3.97 (ddd, *J* = 9.3, 6.1, 3.4 Hz, 1 H), 3.90 (bdd, *J* = 9.9, 2.1 Hz, 1 H), 3.77 (ddd, *J* = 11.2, 11.2, 2.8 Hz, 1 H), 3.69 (bdd, *J* = 9.9, 2.8 Hz, 1 H), 3.59 (ddd, *J* = 11.2, 11.2, 2.8 Hz, 1 H), 3.51-3.41 (m, 2 H), 3.39 (s, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$) δ = 155.8, 130.2, 129.2, 121.5, 120.2, 117.6, 84.3, 68.3, 67.1, 66.4, 57.9, 29.9. IR: 3363, 3054, 2859, 1489, 1457, 1265, 1242, 1123, 1083, 731, 702 cm^{-1}. HRMS $C_{12}H_{16}O_4$ $(M+Na)^+$ calcd. 247.0941, obsvd. 247.0945.

Preparation of Catalyst Complexes

Preparation of Pd[(*S*)- *i*Pr-Quinox]Cl_2

To an oven dried 100 mL round bottom flask equipped with stir bar were added 381 mg of $Pd(MeCN)_2Cl_2$ (1.47 mmol, 1.00 equiv.), 300 mg of (*S*)-*i*Pr-quinox ligand (1.47 mmol, 1.00 equiv.) and 80 mL of DCE under a nitrogen atmosphere. The reaction

mixture was heated at reflux for 10 h. The reaction mixture was then allowed to cool to rt and concentrated to ca. 2 mL. To this mixture, 3 mL of CH_2Cl_2 was added, and precipitation was observed. The remaining solvent was removed in vacuo and dried overnight under vacuum to give the desired complex in quantitative yield (680 mg). $[\alpha]^{20}_D = -57°$ (c = 0.19, $CHCl_3$), ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.59 (d, *J* = 8.7 Hz, 1 H), 8.39 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 7.71 (d, *J* = 8.4 Hz, 1 H), 7.56 (m, 2 H), 5.07 (t, *J* = 10.6 Hz, 1 H), 4.76-4.71 (m, 2 H), 2.89-2.74 (m, 1 H), 0.95 (d, *J* = 6.9 Hz, 3 H), 0.81 (d, *J* = 6.6 Hz, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ = 169.9, 148.7, 145.9, 141.6, 132.3, 131.3, 129.8, 129.5, 127.9, 120.7, 72.1, 67.7, 29.3, 18.8, 14.5. IR: 2958, 1651, 1589, 1371, 923, 839 cm^{-1}.

Preparation of Cu[(*S*)- *i*Pr-Quinox]Cl_2

To an oven dried 50 mL round bottom flask equipped with stir bar were added 45.3 mg of $CuCl_2$ (0.340 mmol, 1.00 equiv.), 81 mg of (*S*)-*i*Pr-quinox ligand (0.34 mmol, 1.0 equiv.) and 16 mL of MeOH under a nitrogen atmosphere. The reaction mixture was heated at reflux for 10 h. The reaction mixture was then allowed to cool to rt and concentrated to ca. 2 mL. Approximately 3 mL of CH_2Cl_2 was added, and precipitation was observed. The remaining solvent was removed in vacuo and dried overnight under vacuum to give complex in quantitative yield (126.3 mg). $[\alpha]^{20}_D = +229$ (c = 0.17, $CHCl_3$), IR: 1651, 1590, 1510, 1254, 1165, 758 cm^{-1}, HRMS $C_{16}H_{24}O_5$ $(M+Na)^+$ calcd. 338.0247, obsvd. 338.0249.

Product Derivatization

Preparation of 58

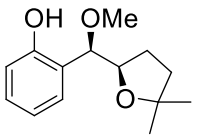
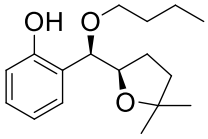
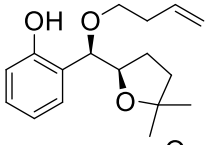
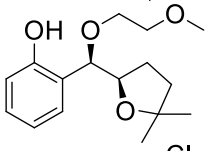
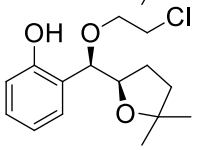
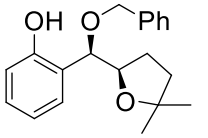
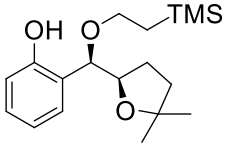
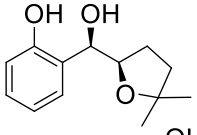
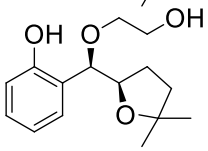
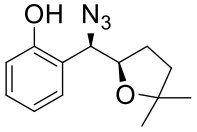
To an oven-dried 5 mL round bottom flask equipped with a stir bar was added 40.0 mg of **55** (0.192 mmol, 1.00 equiv.) in 550:550:820 μL ($MeCN:CCl_4:H_2O$). To the reaction mixture, 4.0 mg of $RuCl_3$ (0.019 mmol, 0.100 equiv.) and 410 mg of $NaIO_4$ (1.92 mmol, 10.0 equiv.) were added at room temperature. After 30 min, the solution was diluted with IPA (500 μL), and the reaction mixture was allowed to stir for another 30 min. The resultant salts were removed by passing the reaction mixture through a celite® plug and an aliquot was concentrated in vacuo. The product **S1** was used without further purification.

To an oven dried 5 mL round bottom flask equipped with a stir bar were added 32.0 mg of **S1** (0.20 mmol, 1.00 equiv.) in 1600:400 μL (CH_2Cl_2:MeOH). To the reaction mixture, 200 μL of $TMSCHN_2$ (0.40 mmol, 2.0 equiv.) was added at 0 °C. After 30 min, the solvent was evaporated in vacuo and the mixture was purified by column chromatography with EtOAc/Hexanes (4% to 10%) as an eluent to give **58** in 45% yield with no loss of diastereomeric ratio observed.

Compound 58 R_f = 0.4 w/ 33% EtOAc/Hexane, colorless liquid, $[\alpha]^D_{20} = -14°$ (c = 0.14, $CHCl_3$), ^{1}H-NMR (500 MHz, $CDCl_3$): 4.20 (aprant q, *J* = 5.25 Hz, 1 H), 3.90 (aprant q, *J* = 6.5 Hz, 1 H), 3.79 (s, 3 H), 3.77-3.74 (m, 2 H), 3.44 (s, 3 H), 1.97-1.83 (m, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 171.3, 83.2, 79.1, 69.1, 59.0, 52.1, 27.4, 26.0, IR: 2956, 1750, 1683, 1558, 1472, 1159 cm^{-1}. HRMS $C_8H_{14}O4$ $(M+Na)^+$ calcd. 197.0784, obsvd 197.0786.

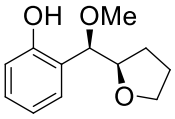
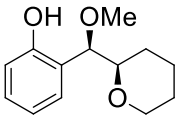
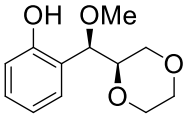
Separation conditions for enantiomers are shown in Table 2.8.

Table 2.8. Separation conditions for determination of enantiopurity.

entry	Compound	Conditions	Retention time	er
1		GC, β-cyclodextrin column 120 °C for 20 min, increase to 140 °C at 0.4 °C/min hold at 140 °C for 2 min, increase to 200 °C at 5 °C/min hold at 200 °C for 8 min	56.8 and 57.9 min	97.9:2.1
2		SFC, 1% Methanol, 3 mL/min Whelko chiral column	3.9 and 4.5 min	96.4:3.6[a]
3		SFC, 1% Methanol, 1 mL/min Whelko chiral column	11.6 and 12.7 min	96.0:4.0[a]
4		SFC, 1% Methanol, 3 mL/min 5 μm Cellucoat chiral column	4.9 and 5.7 min	97.7:2.3
5		SFC, 1% Methanol, 3 mL/min Whelko chiral column	3.7 and 4.3 min	94.0:6.0[a]
6		SFC, 1% Methanol, 3 mL/min Whelko chiral column	7.4 and 8.1 min	96.9:3.1[a]
7		HPLC, 0.5% IPA/Hex, 1 mL/min OJ-H chiral column	29.8 and 32.6 min	99.4:0.6[b]
8		HPLC, 0.5% IPA/Hex, 1 mL/min OJ-H chiral column	29.8 and 32.6 min	98.4:1.6
9		SFC, 1% MeCN, 3 mL/min Cellucoat chiral column	2.5 and 3.9 min	94.9:5.1
10		HPLC, 1% IPA:Hex, 1 mL/min OD chiral column	10.0 and 13.7 min for major 18.5 and 32.9 min for minor	91.9:8.1 91.9:8.1

(a) Product was converted to the corresponding methoxy phenol derivative using KOH and MeI. (b) Product was converted to the free alcohol via deprotection using $BF_3{\cdot}OEt_2$.

Table 2.8. (continued)

entry	Compound	Conditions	Retention time	er
11		SFC, 1% Methanol, 1 mL/min AD-H chiral column	12.2 and 13.7 min	94.8:5.2
12		SFC, 1% Ethanol, 1.5 mL/min Whelko chiral column	12.5 and 14.1 min	94.3:5.7
13		SFC, 1% Methanol, 1.5 mL/min Whelko chiral column	12.3 and 14.1 min	92.0:8.0

Preparation of 59

To an oven-dried 50 mL round bottom flask equipped with a stir bar were added 240.0 mg of **55** (1.010 mmol, 1.000 equiv.) in 7.5 mL MeOH. To the reaction mixture cooled to 0 °C in an ice bath, 720.0 mg of $PhI(OAc)_2$ (2.230 mmol, 2.200 equiv.) in 5 mL of MeOH was added dropwise and warmed to room temperature. After stirring for 90 min, the reaction mixture was then cooled to 0 °C, and solution of saturated Na_2CO_3 was added until precipitate was observed. To this, 20 mL of EtOAc and 5 mL of water were added. The organic layer was separated and washed with water (5 mL) followed by brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was purified with flash silica-gel column chromatography with 10% to 30% EtOAc/Hexanes as eluent to give 215.5 mg of product (73% yield, average of two reactions).

R_f = 0.4 w/ 33% EtOAc/Hexane, colorless liquid, $[\alpha]^{20}_D$ = –42.3° (c = 6.3, $CHCl_3$), ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.83 (dd, J = 3.29 Hz, 0.9 Hz, 1 H), 6.76 (dd, J = 10.2 Hz, 3.3 Hz, 1 H), 6.23 (d, J = 10.2 Hz, 1 H), 4.24 (dd, *J* = 6.2, 0.8 Hz, 1 H), 3.90 (q, *J* = 6.5 Hz, 1 H), 3.35 (s, 3 H), 3.33 (s, 3 H), 3.22 (s, 3 H), 1.70 (m, 4 H), 1.20 (s, 3 H), 1.16 (s, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 185.0, 143.1, 140.6, 137.8, 130.0, 93.0, 81.6, 81.0, 79.1, 57.4, 50.5, 50.4, 38.3, 28.8, 28.2, 28.0, IR: 2967, 2936, 1678, 1644, 1458, 1364, 1109, 1038, 962, 843 cm^{-1}. HRMS $C_{16}H_{24}O_5$ $(M+Na)^+$ calcd. 319.1521, obsvd. 319.1526.

Preparation of 60

The procedure described for **59** was followed, R_f = 0.45 w/ 33% EtOAc/Hexane, colorless liquid, $[\alpha]^{20}_D$ = –57.3° (c = 1.4, $CHCl_3$), ^{1}H-NMR (500 MHz, $CDCl_3$): δ 6.92 (dd,

J = 3.2 Hz, 0.8 Hz, 1 H), 6.82 (dd, J = 10.3 Hz, 3.3 Hz, 1 H), 6.27 (d, J = 10.2 Hz, 1 H), 4.30 (dd, *J* = 5.1 Hz, 0.9 Hz, 1 H), 3.87 (m, 2 H), 3.35 (ddd, J = 4.2 Hz, 1 H), 3.40 (s, 3 H), 3.37 (s, 3 H), 3.30 (s, 3 H), 1.80 (m, 4 H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ 185.2, 143.4, 140.5, 137.6, 130.1, 93.2, 80.9, 78.3, 68.7, 57.8, 50.7, 50.5, 27.6, 26.0, IR: 2940, 2830, 1678, 1644, 1461, 1375, 1116, 962, 843 cm^{-1}. HRMS $C_{14}H_{20}O_5$ $(M+Na)^+$ calcd. 291.1208, obsvd. 291.1202.

Preparation of Mosher Esters (Table 2.9)

To an oven dried 5 mL round bottom flask equipped with a stir bar were added 38.0 mg of **41** (0.170 mmol, 1.00 equiv.) in 1.7 mL THF. To the reaction mixture, 10.0 mg of KOH (0.170 mmol, 1.00 equiv.) and 21 μL of MeI (0.34 mmol, 2.0 equiv.) were added at rt. After 2 h the solution was diluted with EtOAc and washed with water (2 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was used without further purification.

Synthesis of 62 (*R*)-Mosher ester

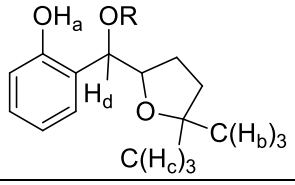
To an oven dried 5 mL round bottom flask equipped with a stir bar were added 20.2 mg of **61** (0.0850 mmol, 2.00 equiv.) in 400 μL CH_2Cl_2. To the reaction mixture, a 19.2 mg of DCC (0.0920 mmol, 2.20 equiv.) 1.5 mg of DMAP (0.30 equiv.) and 10 mg of (*R*)-MTPA (0.043 mmol, 1.0 equiv.) was added at rt. After 2 days, the solution was diluted with EtOAc and washed with solution of saturated NH_4Cl (2 mL) followed by water (2 x 5 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. The product was purified with flash silica-gel column chromatography with EtOAc/hexanes as eluent to give the product in 40% yield. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.56 (d, 2 H), 7.40-7.31 (m, 4 H), 7.05 (dd, *J* = 7.6, 1.6 Hz, 1 H), 6.90-6.84 (m, 2 H),

6.32 (d, *J* = 8.5 Hz, 1 H), 4.32-4.28 (m, 1 H), 3.87 (s, 3 H), 3.63 (s, 3 H), 1.83-1.67 (m, 4 H), 1.30 (s, 3 H), 1.23 (s, 3 H).

Synthesis of 63 (*S*)-Mosher ester

Prepared according to the procedure described above, using (*S*)-MTPA. ^{1}H-NMR (500 MHz, $CDCl_3$) δ = 7.56 (m, 2 H), 7.40-7.27 (m, 4 H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.89 (dd, *J* = 8.3, 0.9 Hz, 1 H), 6.44 (d, *J* = 7.3 Hz, 1 H), 4.26 (ddd, *J* = 7.2, 6.0 Hz, 1 H), 3.86 (s, 3 H), 3.51 (s, 3 H), 1.82-1.57 (m, 4 H), 1.26 (s, 3 H), 1.14 (s, 3 H).

Table 2.9. Difference in chemical shifts for Mosher ester analysis.



H_a	(*S*)-Mosher ester: □ = 3.869	□□^{SR} = +0.005
	(*R*)-Mosher ester: □ = 3.874	
H_b	(*S*)-Mosher ester: □ = 1.259	□□^{SR} = -0.047
	(*R*)-Mosher ester: □ = 1.306	
H_c	(*S*)-Mosher ester: □ = 1.149	□□^{SR} = -0.082
	(*R*)-Mosher ester: □ = 1.231	
H_d	(*S*)-Mosher ester: □ = 6.448	□□^{SR} = +0.132
	(*R*)-Mosher ester: □ = 6.316	

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CHAPTER 3

SYNTHESIS AND PRELIMINARY BIOLOGICAL STUDIES OF 3-SUBSTITUTED INDOLES ACCESSED BY A PALLADIUM-CATALYZED ENANTIOSELECTIVE ALKENE DIFUNCTIONALIZATION REACTION

Introduction

As discussed in Chapter 2, we have discovered a unique method for synthesizing *o*-QM intermediates and utilized it for dialkoxylation reactions of vinyl phenols with simple alcohols. Because *o*-QMs are reactive intermediates, they give us an opportunity to expand the scope of this transformation beyond simple alcohol nucleophiles. Indoles being one of the most commonly found nitrogen-containing heterocycle in natural products[1-3] and drug molecules[4-6] provided the impetus to evaluate them as exogenous nucleophiles in the alkene difunctionalization reaction (Figure 3.1). This would allow for the rapid construction of molecular complexity around the biologically relevant indole framework. Moreover, the product obtained can be transformed into compound **64**, which has a tetracyclic core structure analogous to the core structure of natural products communesin B[7-9] and diazonamide A.[10-12] Communesin B is of particular relevance to our group due to its μM anti-cancer activity against breast cancer cell lines.[7-9]

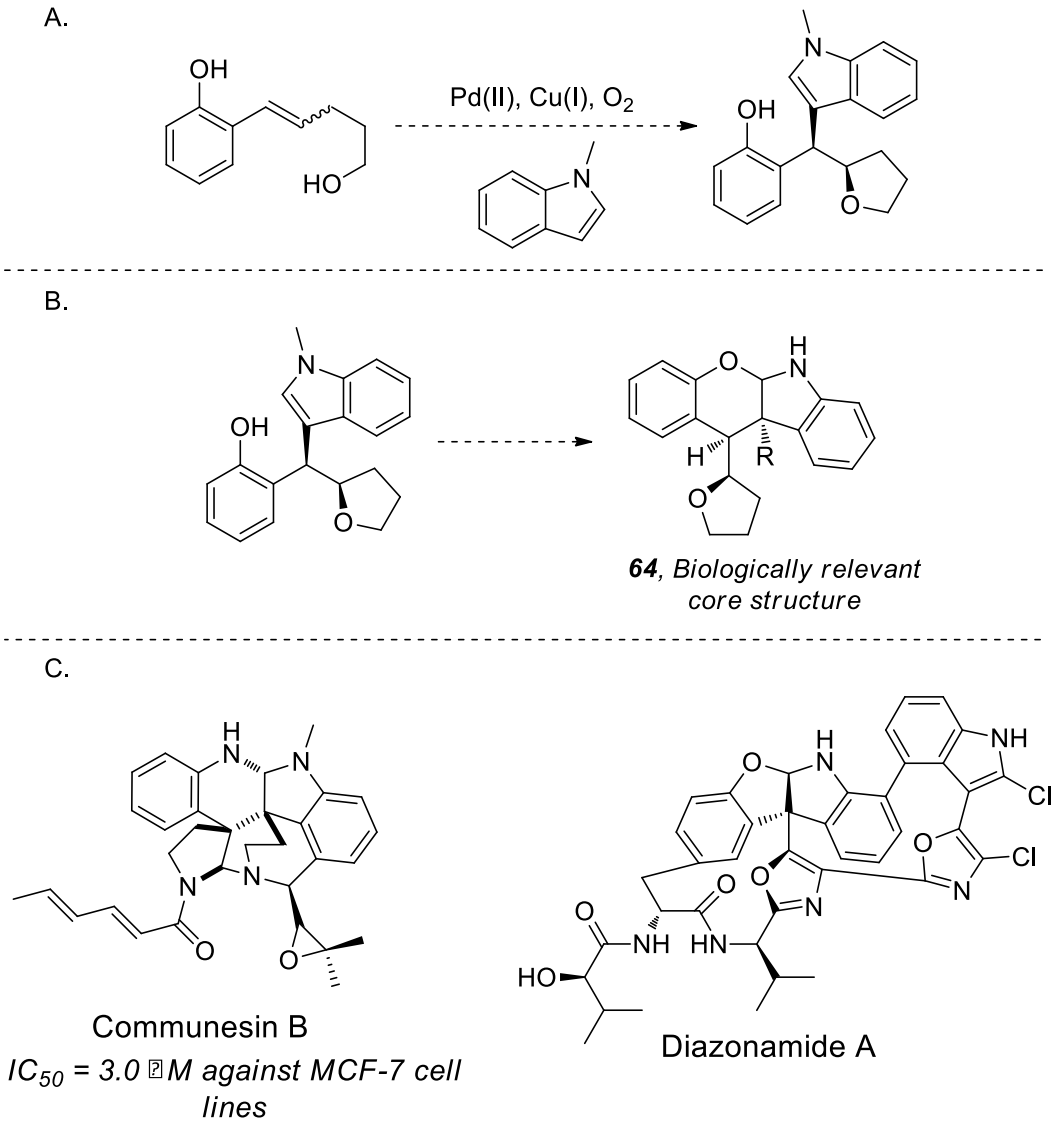


Figure 3.1. Proposed reaction and examples of natural products containing the tetracyclic core structures.

Background

The indole framework represents a privileged structural motif commonly found in pharmaceutical drugs and natural products. Therefore, methods for accessing unique indole derivatives are important for drug-lead synthesis. For this reason, various methods have been developed for functionalization of the indole core. One of the most common methods for functionalization of the indole core is via a Friedel-Crafts alkylation reaction.[13-19] Here, the Pd-catalyzed reactions of heteroaromatics with alkenes are discussed.

Pd-Catalyzed Reaction of Heteroaromatics with Alkenes via Electrophilic Metalation of Heteroaromatic C-H Bonds

In 1999, Fujiwara and coworkers reported a Pd-catalyzed Heck reaction between arenes and alkenes (Figure 3.2).[20] They used benzoquinone (BQ) as a co-oxidant to oxidize Pd^0 to Pd^{II} and *tert*-butyl hydrogen peroxide (TBHP) as a terminal oxidant. The proposed mechanism is shown in Figure 3.2. The aryl-Pd^{II} complex **B** is proposed to form via electrophilic metalation of aromatic C-H bonds. The alkene undergoes insertion to complex **C** followed by β-hydride elimination, leading to product formation and Pd^0, which is oxidized to Pd^{II} by BQ. Later, Gaunt and coworkers utilized a similar concept to develop an intermolecular alkenylation of indoles (Figure 3.3).[21] This work showed alkenylation of an indole can be directed to either the C-2 or C-3 position by simply changing the solvent and terminal oxidant.

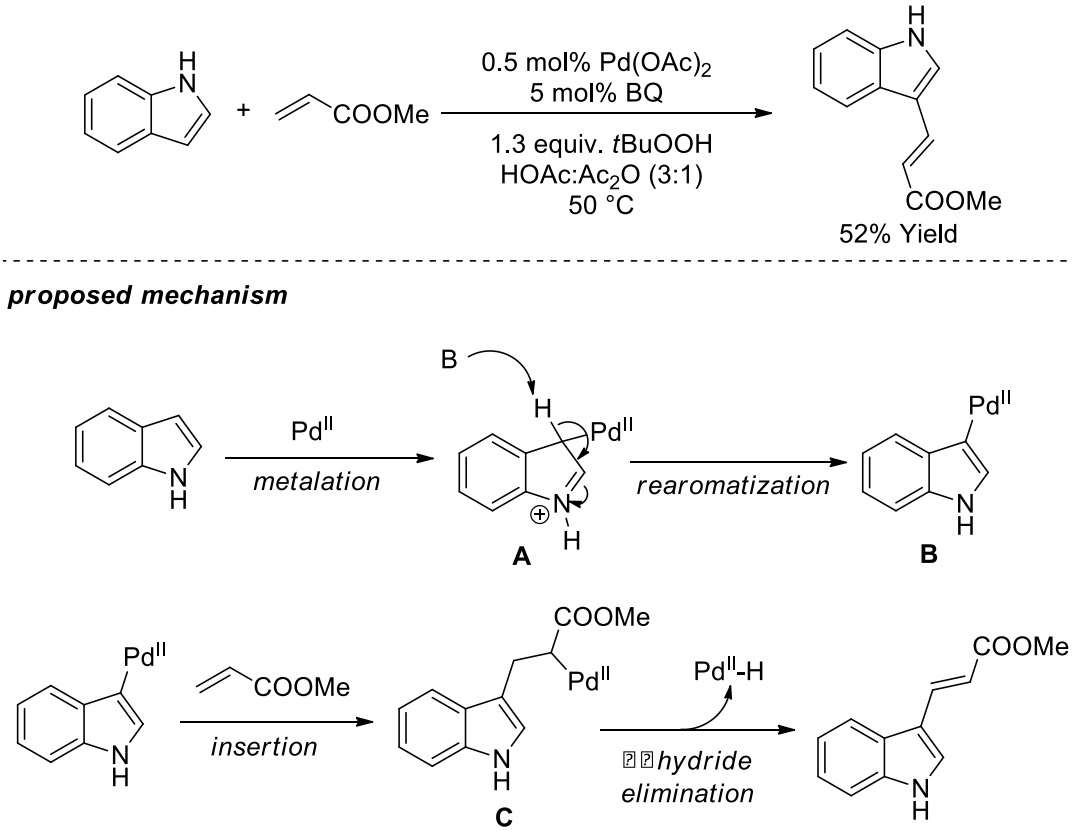


Figure 3.2. Pd-catalyzed Heck reaction of arenes and alkenes. Data from Fujiwara and coworkers.

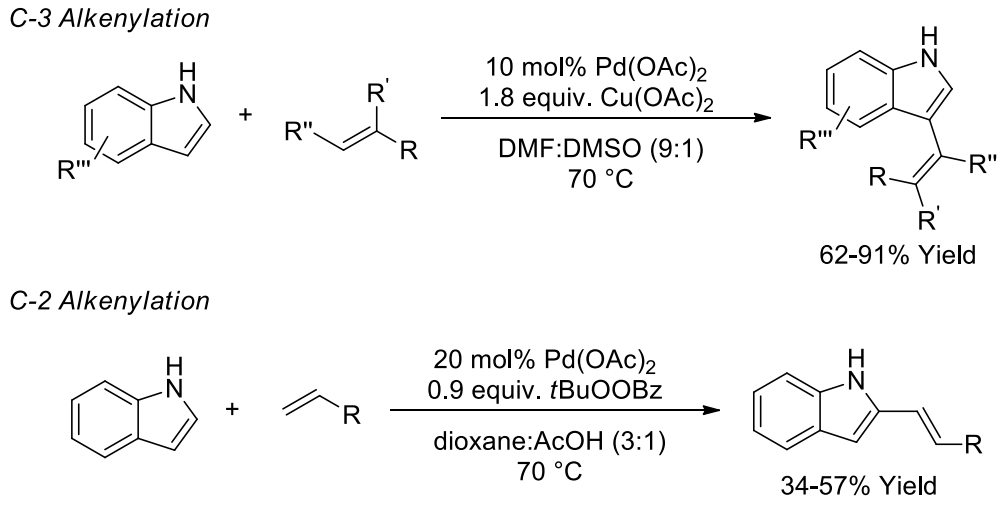


Figure 3.3. Pd-catalyzed alkenylation of indoles. Data from Gaunt and coworkers.

Gaunt and coworkers expanded this methodology to pyrroles, where the protecting group had a substantial impact on alkenylation regioselectivity (Figure 3.4).[22] This method was the key step in an elegant synthesis of Rhazinicine (Figure 3.5).[23] Recently, Zhang and coworkers reported a highly regioselective Pd-catalyzed oxidative coupling of the indolizines and vinylarenes (Figure 3.6).[24] Interestingly, high selectivity for branched products was observed with bidentate nitrogen ligands.

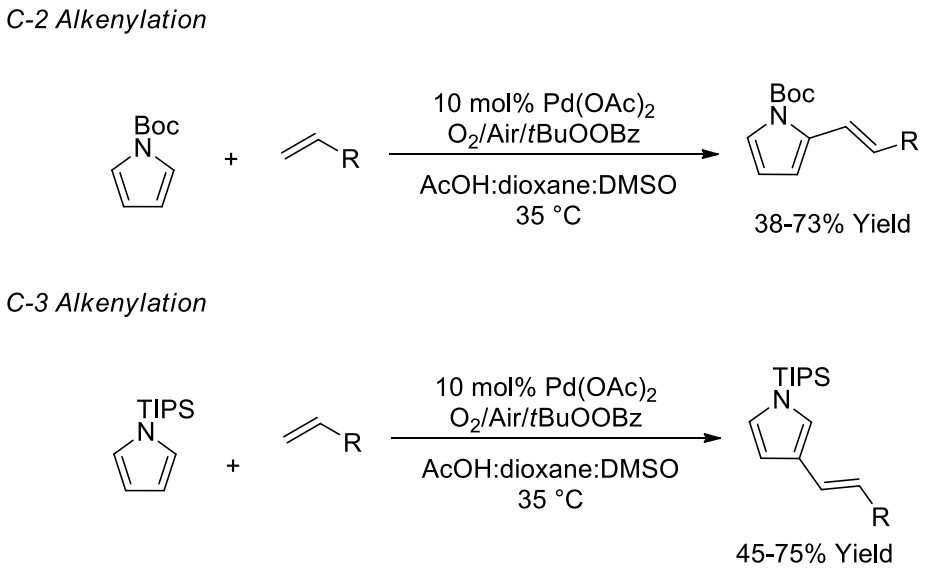


Figure 3.4. Pd-catalyzed alkenylation of pyrroles. Data from Gaunt and coworkers.

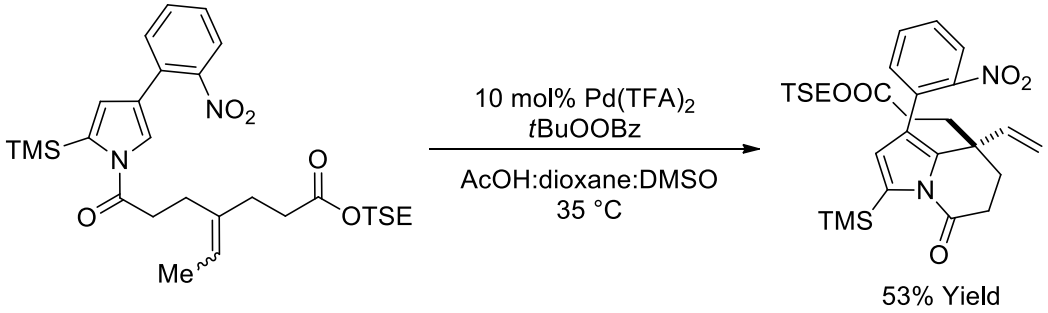


Figure 3.5. Total synthesis of Rhazinicine. Data from Gaunt and coworkers.

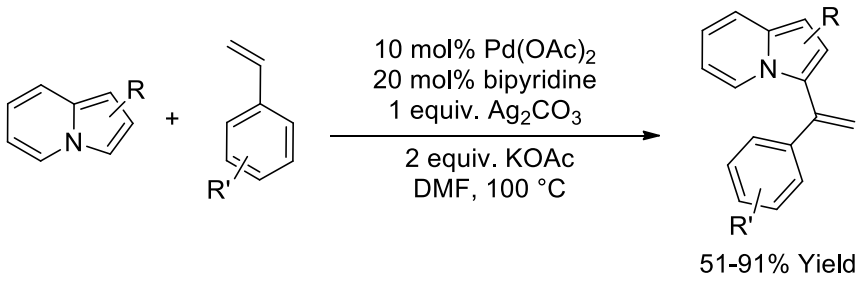


Figure 3.6. Pd-catalyzed alkenylation of indolizines with styrenes. Data from Zhang and coworkers.

Pd-catalyzed Reaction of Indoles with Pd-π-allyl Complexes

Another powerful method for the functionalization of indoles using Pd-catalysis is via reaction of indoles with electrophilic Pd-π-allyl complexes. This mode of reactivity has been explored by various groups to obtaine 3-allyl indoles in both racemic and enantiopure forms. Selected examples of these methods are discussed in this section.

In 2005, Tamaru and coworkers reported a Pd-catalyzed allylation of indoles with allyl alcohols (Figure 3.7).[25] In this reaction, triethylborane (Et_3B) was used as a promoter. The scope of this transformation was found to be broad with excellent yields of the desired products. Later, Trost and coworkers reported an enantioselective variant of this reaction (Figure 3.8),[26] wherein 3-substituted indoles were used to obtain 3,3-disubstituted products in excellent enantioselectivity and good yield. Using 9-BBN(C_6H_{11}) as a promoter and **64** as a chiral ligand was found to give optimal results. Trost and coworkers utilized this method to synthesize the simple alkaloid (—)-esermethole, which contains a quaternary center at 3-position of the indoline ring.

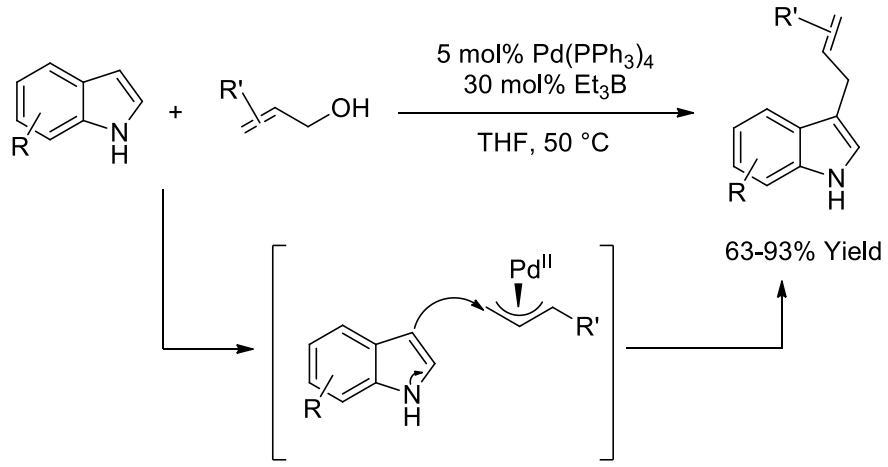


Figure 3.7. Allylation of indoles with allylic alcohols. Data from Tamaru and coworkers.

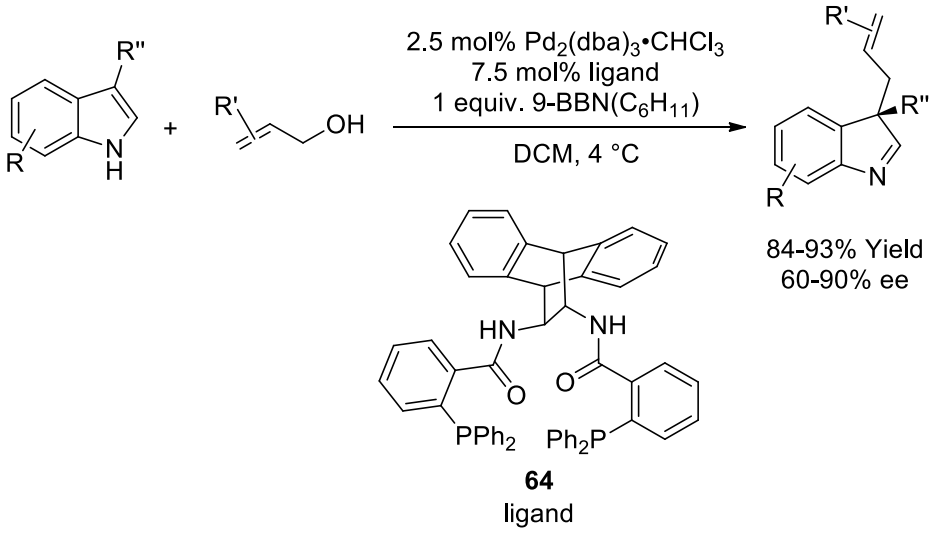


Figure 3.8. Enantioselective allylation of indoles with allylic alcohols. Data from Trost and coworkers.

In the same year, Bandini and coworkers reported an enantioselective intramolecular allylic alkylation of indoles using similar types of chiral ligands (Figure 3.9a).[27] The reaction provides tetrahydro-α-carbolines and tetrahydro-γ-carbolines in good yields and excellent enantioselectivity, using allyl carbonates as the precursor to the Pd-π-allyl complex. Rawal and coworkers also utilized allyl carbonates as a precursor to the Pd-π-allyl complex for allylation of 2,3-disubstituted indoles (Figure 3.9b).[28]

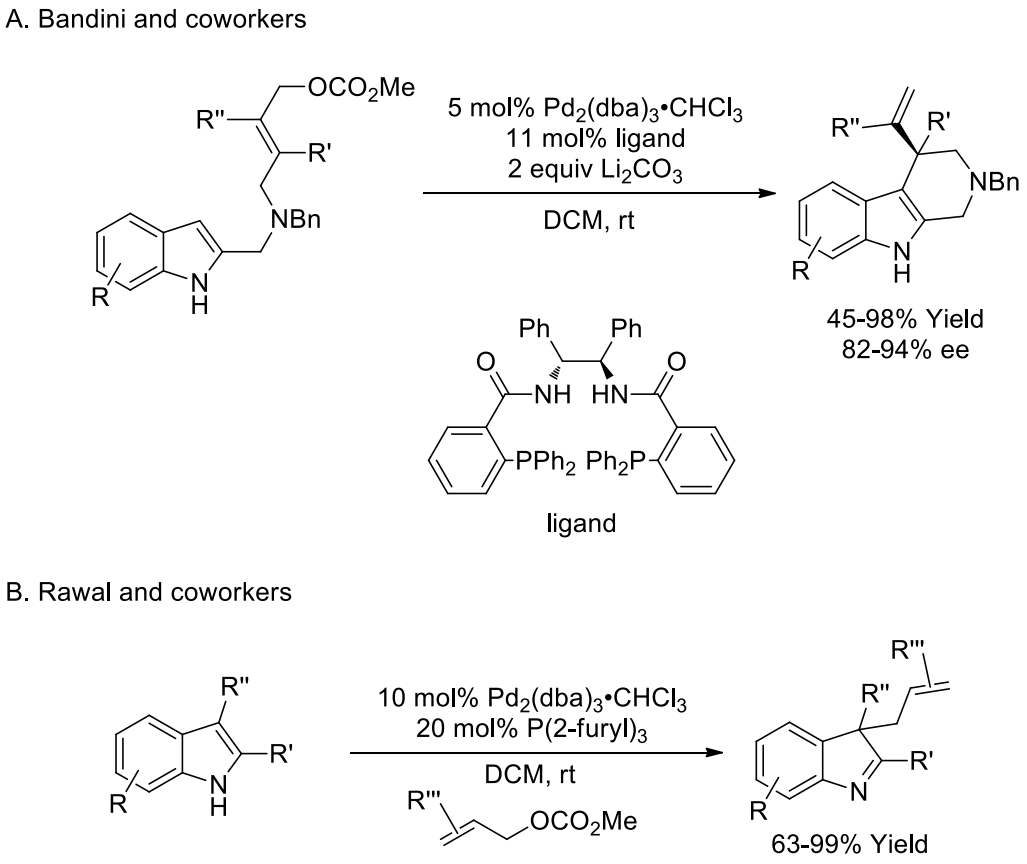


Figure 3.9. Enantioselective intramoleculat allylation of indole with allyl carbonate.

Recently, Trost and coworkers reported an interesting reaction of indoles and pyrroles with Pd-π-allyl intermediates, generated from vinyl aziridines, to give *N*-substituted allyl heterocycles (Figure 3.10).[29] The reaction is highly enantioselective with broad substrate scope. However, protecting groups on the aziridine are limited to Bn (benzyl) and PMB (*p*-methoxybenzyl) groups. This method's utility was further demonstrated in the synthesis of natural products longamide B, longamide B methyl ester, hanishin, ageaamide A, agesamide B and cyclooroidin.

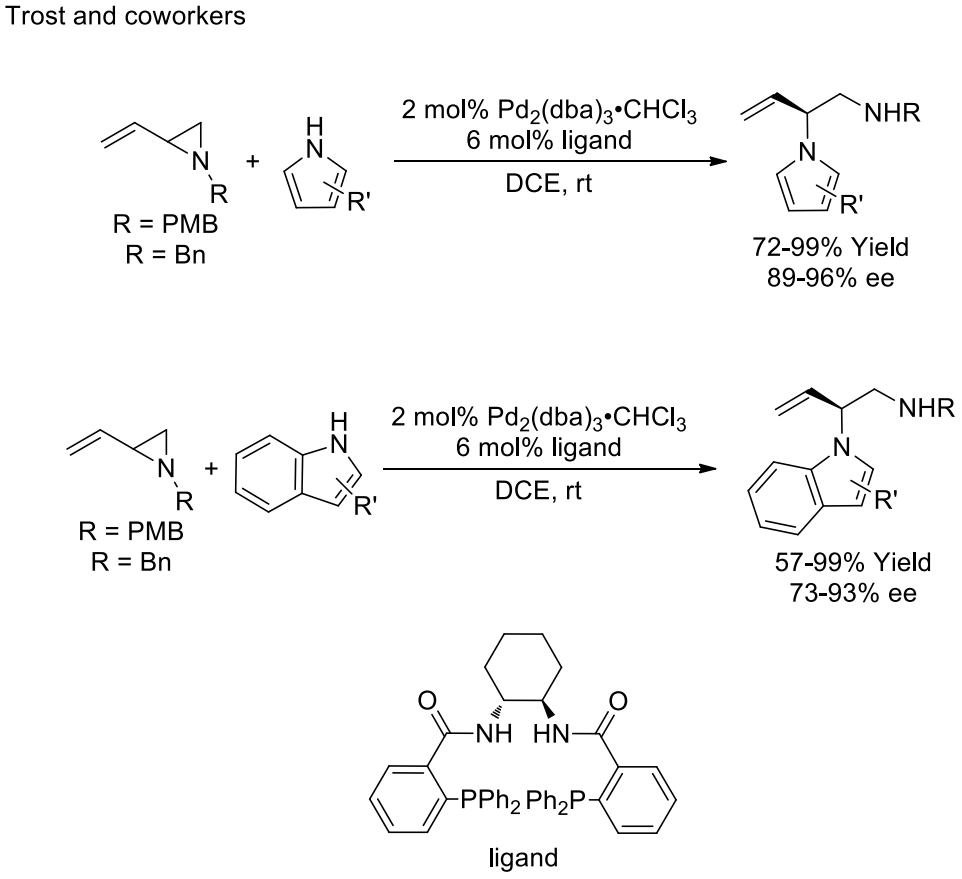


Figure 3.10. Pd-catalyzed enantioselective *N*-alkylation of indoles and pyrroles Data from Trost and coworkers.

Reaction of *o*-QM with Heteroaromtics

o-QMs are highly reactive intermediates and their reaction with various nucleophiles has been published. However, reports of reactions of heteroaromatics with *o*-QMs are limited. The most recent report came in 2006 from Kaïm and coworkers, wherein they described a novel method to synthesize *o*-QM in situ (Figure 3.11). Aldehydes were reacted with amines and phenols to give Mannich adducts like **65**, which were treated with dibromoethane in the presence of a Lewis acid to give the *o*-QMs. Subsequently, the *o*-QM was reacted with *N*-Me-indole to give the desired product **66**. It should be noted that only two examples are reported in this paper.

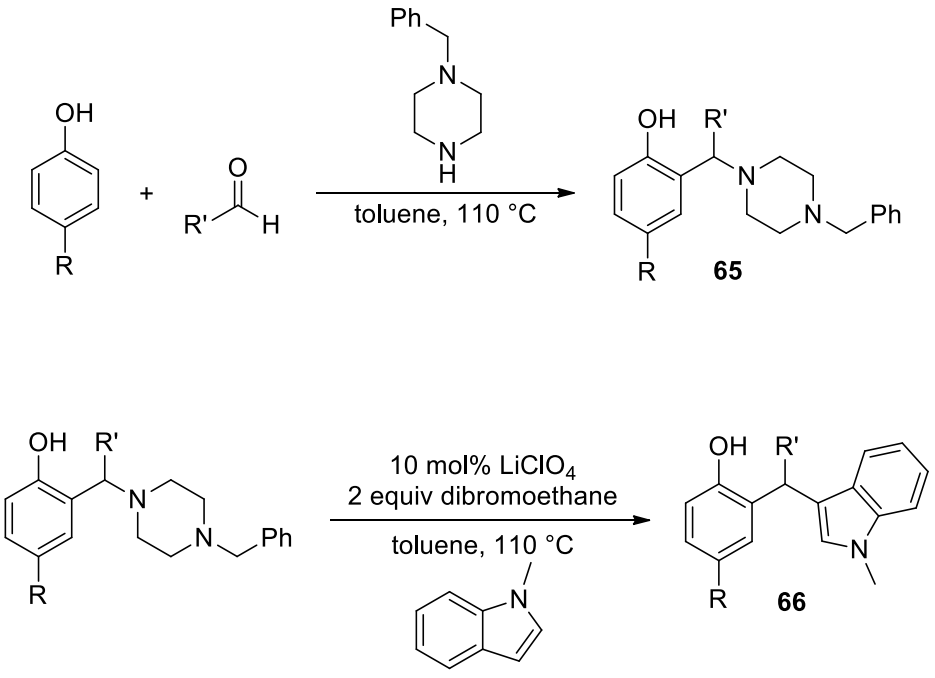


Figure 3.11. Recent example of *o*-QM reaction with indole.

Results and Discussion

As described in Chapter 2, we have developed a sequential intramolecular/ intermolecular dialkoxylation reaction. Desiring to further expand the scope of this process, other nucleophiles were explored. Indole being a prevalent heterocycle in pharmaceuticals and natural products, it was chosen as a preferred nucleophile to study. The proposed reaction mechanism for the formation of the desired product, using heteroaromatics as nucleophiles, is shown in Figure 3.12. We proposed the substrate would undergo an intramolecular nucleopalladation, with subsequent formation of a reactive *o*-QM intermediate **A**. To this intermediate, addition of electron-rich heteroaromatic derivatives could be accomplished, via electrophilic aromatic substitution, to give intermediate **B**. Rearomatization of **B** would give the desired product.

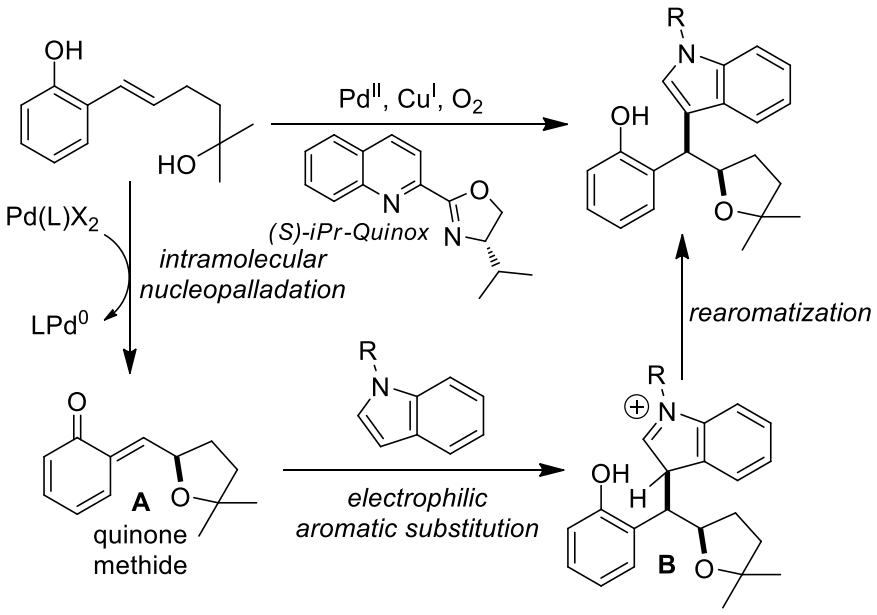
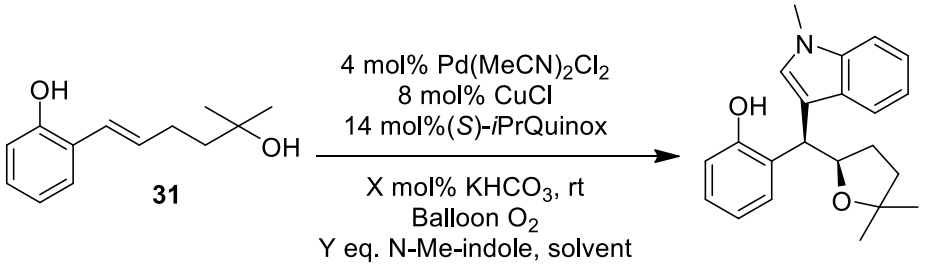


Figure 3.12. Proposed mechanism of Pd-catalyzed sequential intra- intermolecular reactions with indoles.

When *N*-Me-indole was treated with substrate **31** under similar conditions to the previous report, it gave the desired product in 61% yield with excellent enantio- and diastereoselectivity (Table 3.1, entry 1). Encouraged by this result, further optimization of the reaction conditions was conducted. Increasing the amount of base and using a mixture of 4:1 toluene:THF gave a slightly increased yield and enantioselectivity of the desired product (Table 3.1, entries 2-3). Finally, addition of 15 equivalents of nucleophile provided the optimal conditions, giving an 81% yield of the desired product and excellent enantioselectivity and diastereoselectivity (Table 3.1, entry 4). It should be noted that 5 equivalents of indole also gave the desired product, albeit in lower yield, without any deterioration of enantioselectivity or diastereoselectivity (Table 3.1, entry 5).

Table 3.1. Optimization of the reaction conditions.



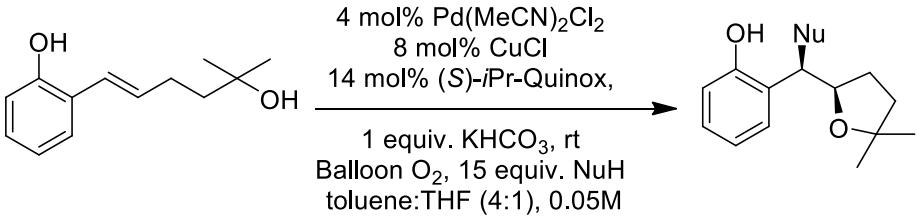
Entry	X	Y	Solvent	% Yield[a]	er[b]	dr[c]
1	40	10	Toluene	61	95.5:4.5	>20:1
2	100	10	Toluene	64	95.5:4.5	>20:1
3	100	10	Toluene:THF (4:1)	65	97:3	>20:1
4	100	15	Toluene:THF (4:1)	81	97:3	>20:1
5	100	5	Toluene:THF (4:1)	61	97:3	>20:1

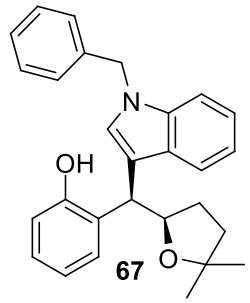
a) isolated yield, b) measured using SFC, c) measured by ^{1}H-NMR

Having identified the optimized conditions, the scope of the alkene difunctionalization reaction was explored. Beginning with the exogenous nucleophile, it was found that *N*-alkyl-protected indoles were well tolerated, including an indole containing a removable protecting group (Table 3.2, compounds **67** and **68**). Various 2-substituted indoles with varied steric and electronic parameters were also found to be compatible, leading to good yields and excellent enantioselectivity (Table 3.2, compounds **69**-**71**). As evidenced by compounds **72**-**75**, the electronic nature of indole ring substituent had little effect on the reaction outcome. Additionally, 5-bromoindole was tolerated, giving a 62% yield and an excellent enantiomeric ratio (er) of 98:2 (Table 3.2, compounds **73**). This result showcases the potential for further functionalization of these compounds with Pd^0 catalysis. Furthermore, the chemistry presented is not limited to only indole as a nucleophilic heterocycle, as demonstrated by the successful use of *N*-methylpyrrole (Table 3.2, compound **76**). A caveat to this chemistry is the requirement of *N*-protection of the indole, with the electron-poor protecting groups (such as Ts or Boc) substantially decreasing the yield.

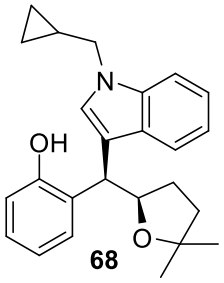
Next**,** in exploring vinyl phenols, it was found that electron-withdrawing substituents generally gave higher yields. High diastereoselectivity and enantioselectivity were observed in all cases (Table 3.3, compounds **78**-**82**). Both tetrahydrofuran and tetrahydropyran ring systems were formed in good yields with excellent er and diastereomeric ratio (dr) (Table 3.3, compounds **83** and **84**). A 1,4-dioxane product was also generated, albeit in modest yield, from a substrate containing an ether linkage (Table 3.3, compound **85**).

Table 3.2. Scope of exogenous nucleophiles.

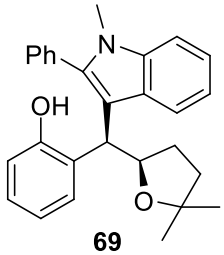




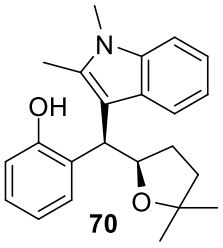
58% Yield
97:3 er, 12 h



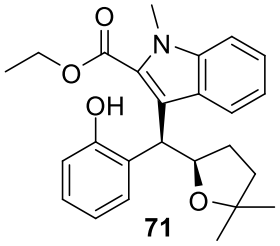
61% Yield
98.5:1.5 er, 16 h



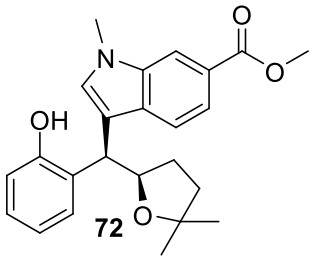
61% Yield
98.5:1.5 er, 8 h



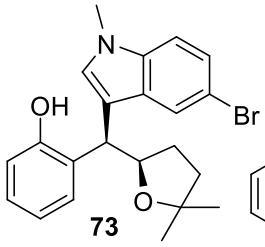
70% Yield
98.5:1.5 er, 8 h



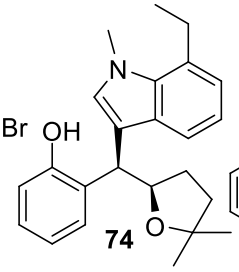
51% Yield
98.5:1.5 er, 12 h



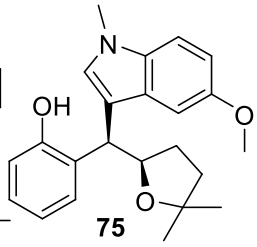
50% Yield
98:2 er, 8 h



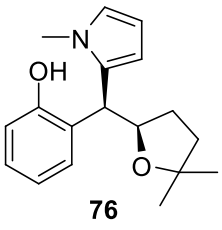
62% Yield
98:2 er, 6 h



65% Yield
98.5:1.5 er, 10 h



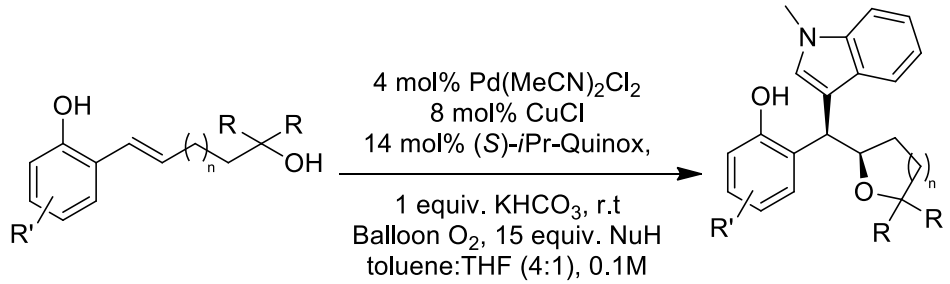
57% Yield
99:1 er, 3 h

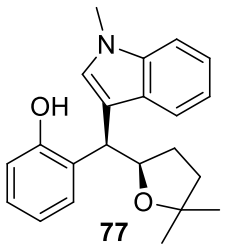


53% Yield
92.5:7.5 er, 4 h

er for major diastereomer determined by SFC using a column equipped with a chiral stationary phase. dr ⍰ 20:1 for all compounds. dr determined by ^{1}H NMR. Major diastereomer determined by X-ray crystal analysis of entry **73.** Absolute configuration was assigned by comparison with a previous report.

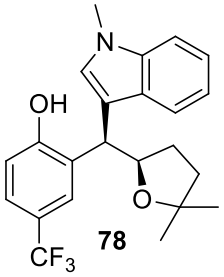
Table 3.3. Scope of phenols and intramolecular nucleophiles.





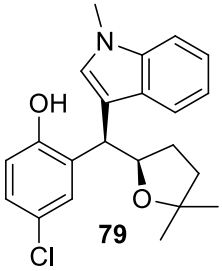
77

81% Yield, 3 h
97:3 er



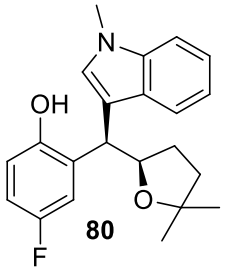
78

72% Yield, 4 h
95.5:4.5 er



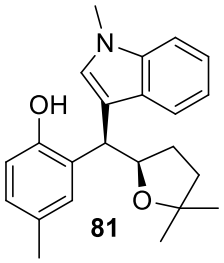
79

87% Yield, 4 h
98:2 er



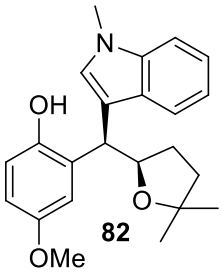
80

78% Yield, 6 h
95:5 er



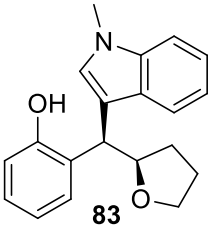
81

58% Yield, 8 h
95.5:4.5 er



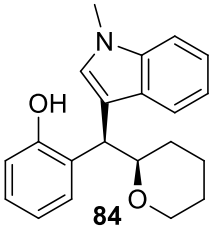
82

44% Yield, 4 h
94.5:5.5 er



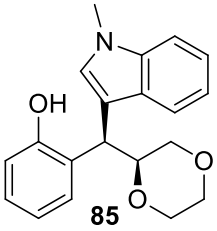
83

82% Yield, 5 h
97:3 er



84

62% Yield, 12 h
92.5:7.5 er



85

30% Yield, 36 h
92:8 er

er for major diastereomer determined by SFC using a column equipped with a chiral stationary phase. dr ⍰ 20:1 for all compounds. dr determined by ^{1}H NMR. Major diastereomer determined by X-ray crystal analysis of entry **73.** Absolute configuration was assigned by comparison with previous report.

Product Derivatization

With the goal of showcasing the utility of the product's phenol moiety for synthesizing tetracyclic core structures, which resembles the core of the communesin natural product class, further derivatization of **83** was performed (Figure 3.13). Treatment of **83** with NBS resulted in rapid oxidative cyclization, affording **86** as the fused tetracyclic product in 92% yield.[30] Additionally, treatment of **83** with DMDO resulted in the formation of the tertiary alcohol **87** in good yield, albeit with low dr.[31] Compound **87**, which has homology with the core structure of the communesin class of natural products[32] and contains four contiguous stereocenters can be synthesized from salicylaldehyde in just four steps. This clearly demonstrates the utility of this method to rapidly access a relatively complex molecular scaffold.

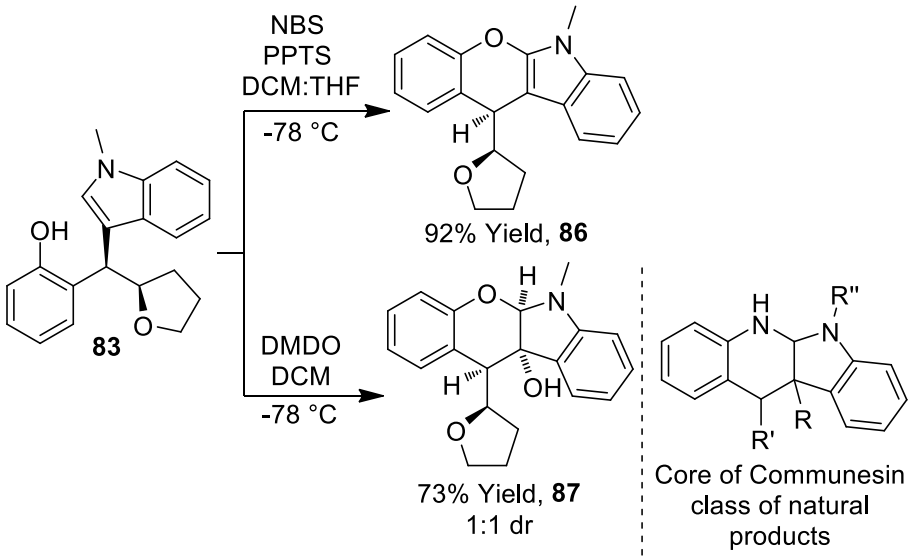


Figure 3.13. Product derivatization to provide tetracyclic frameworks.

Biological Study

In view of the ease with which we were able to access diverse analogues and the unique architecture of the products formed, we chose to evaluate the biological activity of several racemic variants using a luminal-type breast cancer cell line (MCF-7). These studies were performed by Prof. Matthew S. Sigman and Dr. Keith M. Gligorich in the laboratory of Prof. Brian Welm at the Huntsman Cancer Institute. Excitingly, various compounds were found to be cytotoxic with moderate to good selectivity for cancerous cells over normal cells. Interestingly, tetracyclic compound **87**, which resembles the core of communesin B, did not show any toxicity towards cancer cells (Figure 3.14). On the other hand, compound **72** is more effective than natural product communesin B. This is encouraging, since compound **72** is structurally simpler than communesin B and is also more modular. Of most interest, compounds **69** and **72** showcased different phenotypes, when cell cycle analysis was performed. It was observed that compound **69** caused a G1 arrest while **72** caused a G2 arrest similar to that induced by taxol (Figure 3.15). This finding suggests that modest structural changes in the indole framework have a significant bearing on the molecular target of these compounds. Currently, we are performing further biological studies to understand the mode of action of these two promising compounds.

Determination of Product Stereochemistry

The relative stereochemistry was determined by X-ray crystal analysis of compound **73**, and the absolute configuration was assigned based on analogy with our previous report (Figure 3.16).

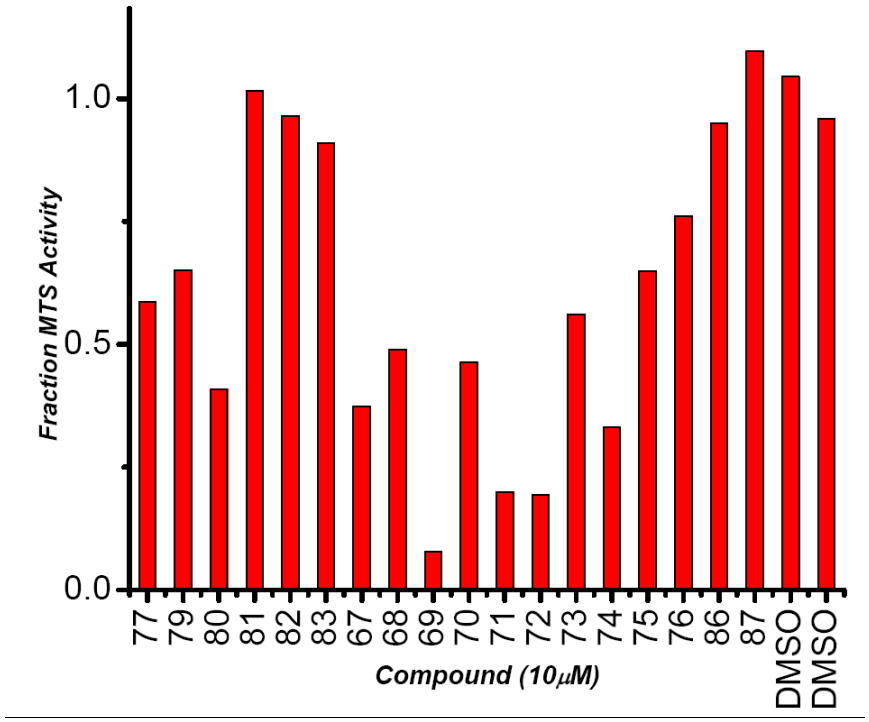


Figure 3.14. Biological activity of compounds against MCF-7 cell lines.

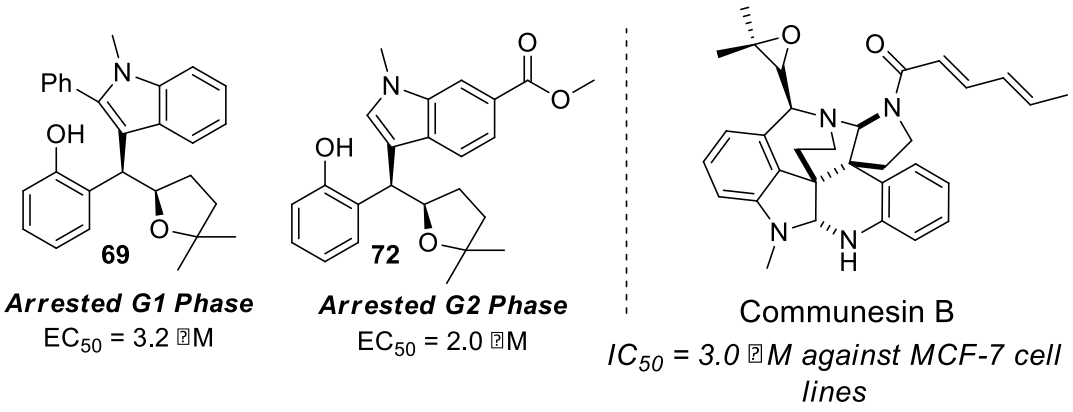


Figure 3.15. Comparison of biological activity of **69** and **72** with communesin B.

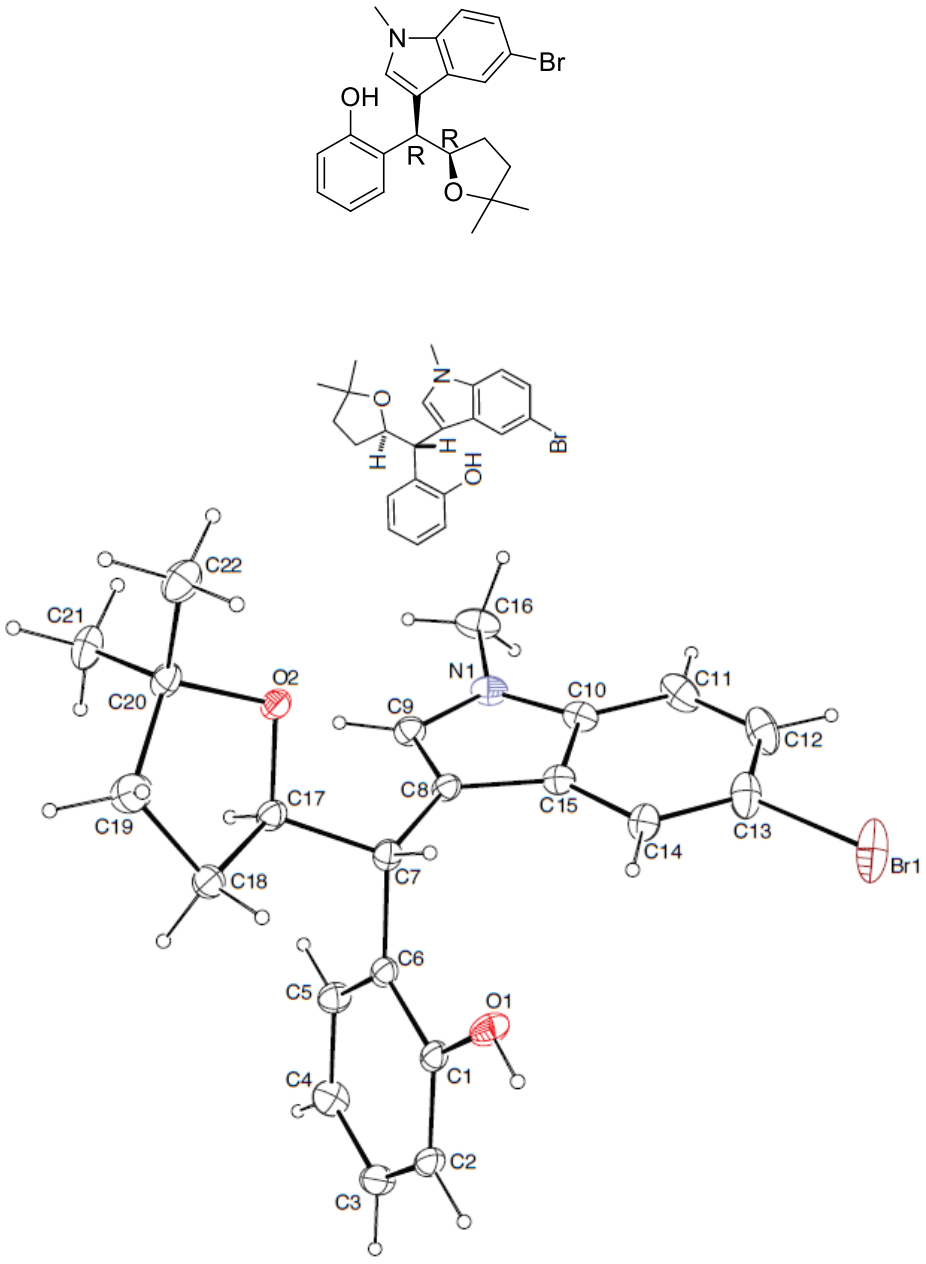


Figure 3.16. X-ray of compound **73**.

Conclusion

We have developed a highly enantioselective alkene difunctionalization with indoles as an exogenous nucleophiles, furnishing 3-substituted indoles in excellent yield and stereoselectivity.[33] The products obtained can be readily processed to biologically relevant tetracyclic core structures. Moreover, the newly synthesized 3-substituted indoles demonstrated encouraging μM activity against breast cancer cell lines. Currently, further studies on the mode of action of these compounds and improvement of their selectivity and cytotoxicity are underway.

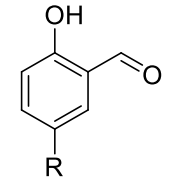
Experimentals

General Information

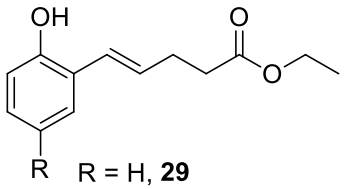
Unless otherwise noted, all reactions were run under a nitrogen atmosphere with stirring. Toluene, dichloromethane, and THF were dried before use by passing through a column of activated alumina. Triethylamine was distilled from CaH_2. All other reagents (including indoles) were purchased from commercial sources and used without further purification. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained either with potassium permanganate, *p*-anisaldehyde, phosphomolybdic acid, or ninhydrin. Flash column chromatography was performed with EcoChrom MP Silitech 32-63D 60Å silica gel, slurry packed with solvents indicated in glass columns. Nuclear magnetic resonance spectra were acquired at 400 MHz for ^{1}H, and 100 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million downfield relative to the line of $CHCl_3$ singlet at 7.26 ppm. Chemical

shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center-line of the $CDCl_3$ triplet at 77.2 ppm. The abbreviations s, d, t, q, td, dd and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, triplet of doublet, doublet of doublet and multiplet, respectively. Optical rotations were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length. Concentrations are reported in g/100 mL. IR spectra were recorded using a Nicolate FTIR instrument. SFC (super critical fluid chromatography) analysis was performed at 40 °C and 200 bar backpressure, using a Thar instrument fitted with chiral stationary phase (as indicated). Glassware for all reactions was oven-dried at 110 ^{o}C and cooled while purging with nitrogen prior to use.

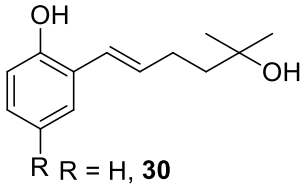
Substrate Synthesis



R = H, **28**
R = CF_3, **4.S$_1$**
R = F, **4.S$_2$**
R = Cl, **4.S$_3$**
R = Me, **4. S$_4$**
R = OMe, **4.S$_5$**



R = H, **29**
R = F, **88**
R = Cl, **89**
R = Me, **90**
R = OMe, **91**



R = H, **30**
R = CF_3, **92**
R = F, **93**
R = Cl, **94**
R = Me, **94**
R = OMe, **96**

Preparation of 29

To an oven-dried 500 mL round bottom flask equipped with a stir bar were added 23.4 g of **27** (51.0 mmol, 2.30 equiv.) and 200 mL toluene. To this was added a solution of 5.80 g KO^{t}Bu (51.2 mmol, 2.33 equiv.) in 40 mL of THF dropwise via cannulation. The reaction mixture slowly turned a deep red color over 4 h. The mixture was cooled to

–78 °C and 2.70 g of salicylaldehyde **28** (22.2 mmol, 1.00 equiv.), dissolved in 20 mL of toluene, was added dropwise via cannulation. The mixture was allowed to slowly warm to ambient temperature and stirred 48 h then quenched with 50 mL of saturated NH_4Cl solution. The mixture was diluted with 100 mL of diethyl ether and washed with 100 mL (2 x 50 mL) of water and 60 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 10%-20% EtOAc/Hexanes as eluent to give 4.15 g of **29** (85% yield, average of two reactions). Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.52 w/ 33% EtOAc/Hexane, colorless oil, ^{1}H-NMR (300 MHz, $CDCl_3$) δ = 7.02-7.28 (m, 2 H), 6.85-6.95 (m, 2 H), 6.38-6.48 (d, *J* = 11.2 Hz, 2 H), 5.89 (s, 1 H), 5.74-5.86 (m, 1 H), 4.08-4.16 (m, 2 H), 2.37-2.48 (m, 4 H), 1.18-1.29 (m, 3 H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ = 173.3, 153.1, 134.4, 129.9, 128.8, 125.1, 123.8, 120.5, 116.1, 60.9, 33.9, 24.3, 14.3. IR 3392, 2981, 1705, 1450, 1269, 1195, 1154, 754 cm^{-1}. HRMS $C_{13}H_{16}O_3$ $(M+Na)^+$ calcd. 243.0997, obsvd. 243.0996.

Preparation of 89

The same procedure as that of **29** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.32 w/ 20% EtOAc/Hexane, colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.09 (dd, *J* = 8.6 Hz, *J* = 2.6 Hz, 1 H), 7.04 (d, *J* = 2.6 Hz, 1 H), 6.82 (d, *J* = 8.6 Hz, 1 H), 6.34 (d, *J* = 11.3 Hz, 1 H), 6.29 (s, 1 H), 5.79 (dt, *J* = 11.3 Hz, *J* = 6.9 Hz, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.47-2.37 (m, 4 H), 1.23 (t, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ = 173.8, 151.7, 134.9, 129.4, 128.6, 125.3, 124.9, 124.2, 117.3, 61.1, 33.6, 24.2, 14.3. IR 3392, 2980, 1702, 1478, 1269, 1195, 1148, 814 cm^{-1}. HRMS $C_{13}H_{15}O_3Cl$ $(M+Na)^+$ calcd. 277.0607, obsvd. 277.0618.

Preparation of 88

The same procedure as that of **29** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.32 w/ 20% EtOAc/Hexane, colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.85-6.77 (m, 2 H), 6.37 (dd, *J* = 11.1 Hz, *J* = 6.4 Hz, 1 H), 6.01 (d, *J* = 39.4 Hz, 1 H), 5.84-5.77 (m, 1 H), 4.13 (q, *J* = 7.2 Hz, 2 H), 2.47-2.36 (m, 4 H), 1.23 (t, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ = 173.1, 157.9, 149.1, 134.9 (d), 124.4 (d), 116.8 (q), 115.8 (q), 115.2 (q), 61.0, 34.7, 24.2, 14.3. IR 3392, 2980, 1702, 1478, 1269, 1195, 1148, 814 cm^{-1}. HRMS $C_{13}H_{15}O_3F$ $(M+Ag)^+$ calcd. 345.0056, obsvd. 345.0081.

Preparation of 90

The same procedure as that of **29** was followed**,** Isomeric ratio (E/Z): 10:1, Major isomer: R_f = 0.42 w/ 33% EtOAc/Hexane, colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 6.98 (d, *J* = 8.2 Hz, 1 H), 6.93 (s, 1 H), 6.83 (dd, *J* = 8.2 Hz, *J* = 0.8 Hz, 1 H), 6.47 (d, J = 11.2 Hz, 1 H), 5.84-5.77 (m, 1 H), 4.17 (q, J = 8.3 Hz, 2 H), 2.49-2.47 (m, 4 H), 2.30 (s, 3 H) 1.27 (t, J = 8.3 Hz, 3 H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ = 173.7, 150.8, 133.4, 130.2, 129.3, 125.4, 123.5, 115.7, 60.8, 33.9, 28.2, 24.2, 20.7. IR 3411, 2981, 1711, 1494, 1178, 906, 787, 726 cm^{-1}. HRMS $C_{14}H_{18}O_3$ $(M+Na)^+$ calcd. 257.1154, obsvd. 257.1165.

Preparation of 91

The same procedure as that of **29** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.30 w/ 20% EtOAc/Hexane, colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.02 (d, *J* = 8.2 Hz, 1 H), 6.60 (s, 1 H), 6.46-6.39 (m, 3 H), 5.66 (dt, *J* = 11.8 Hz, *J* = 6.2 Hz, 1 H), 4.11 (q, *J* = 7.2 Hz, 2 H), 3.73 (s, 3 H), 2.40-2.48 (m, 4 H), 1.22 (t, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (75 MHz, $CDCl_3$) δ = 174.6, 154.3, 147.0, 134.3, 130.6, 124.9,

116.8, 114.3, 60.9, 55.4, 34.1, 24.3, 14.3. IR 3408, 2980, 1729, 1492, 1197, 1145, 808 cm^{-1}. HRMS $C_{14}H_{18}O_4$ $(M+Na)^+$ calcd. 273.1103, obsvd. 273.1111.

Preparation of 30

To an oven dried 500 mL round bottom flask equipped with a stir bar were added 4.10 g of **29** (18.6 mmol, 1.00 equiv.) in 180 mL THF. To this was slowly added a solution of 3.0 M MeMgBr (130 mmol, 7.00 equiv.) at 0 °C. The reaction mixture was then allowed to warm to room temperature and was stirred for 12 h. The reaction was quenched by the slow addition of 20 mL of 1 M HCl solution. The mixture was diluted with 50 mL of diethyl ether and washed with 100 mL (2 x 50 mL) of water and 60 mL of brine. The organic extract was dried over $MgSO_4$, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 1 L of 50% Hexane/EtOAC as eluent to give 3.34 g of **30** in 87% yield. Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.32 w/ 33% EtOAc/Hexane, colorless solid. MP = 74-75 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.28-7.07 (m, 2 H), 6.95-6.87 (m, 2 H), 6.40-6.37 (d, *J* = 10.9 Hz), 5.95-5.88 (m, 1 H), 5.34 (s, 1 H), 2.28-2.19 (m, 2 H), 1.67-1.57 (m, 2 H), 1.19 (s, 6 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 152.9, 137.0, 129.8, 128.8, 123.9, 123.4, 120.4, 115.5, 71.3, 43.3, 29.4, 24.1. IR 3410, 3013, 2971, 1604, 1448, 1377, 1261, 1210, 1147, 1131, 904, 755 cm^{-1}. HRMS $C_{13}H_{18}O_2$ $(M+Na)^+$ calcd. 229.1204, obsvd. 229.1201.

Preparation of 92

The same procedure as that of **30** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.32 w/ 33% EtOAc/Hexane, colorless solid. MP = 121-122 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.46-7.38 (m, 2 H), 6.98 (d, *J* = 8.4 Hz, 1 H), 6.37 (*d*, *J* = 11.2 Hz),

6.0 (dt, *J* = 11.2 Hz, *J* = 7.4 Hz, 1 H), 2.25-2.19 (m, 2 H), 1.67-1.57 (m, 2 H), 1.19 (s, 6 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 155.8, 138.3, 127.2, 127.1, 126.0, 125.9, 124.3, 122.3, 115.8, 71.7, 42.9, 29.4, 24.2. IR 3247, 2970, 1612, 1442, 1324, 1283, 1107, 1073, 906, 783 cm^{-1}. HRMS $C_{14}H_{17}O_2F_3$ $(M+Na)^+$ calcd. 297.2606, obsvd. 297.2617.

Preparation of 93

The same procedure as that of **30** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.20 w/ 20% EtOAc/Hexane, colorless solid. MP = 102-103 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.01 (dd, J = 8.6 Hz, J = 2.6 Hz, 1 H), 7.06 (d, J = 2.6 Hz, 1 H), 6.81 (d, *J* = 8.6 Hz), 6.28 (d, J = 11.2 Hz, 1 H), 5.94-5.89 (m, 1 H), 2.21-2.16 (m, 2 H), 1.61-1.58 (m, 2 H), 1.19 (s, 6 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 151.7, 137.7, 129.4, 128.5, 125.6, 124.9, 122.5, 116.3, 71.6, 42.9, 29.4, 24.1. IR 3455, 2964, 1604, 1468, 1375, 1254, 1210, 1136, 926, 775 cm^{-1}. HRMS $C_{13}H_{15}O_2Cl$ $(M+Na)^+$ calcd. 263.0815, obsvd. 263.0801.

Preparation of 94

The same procedure as that of **30** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.30 w/ 20% EtOAc/Hexane, colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85-6.79 (m, 3 H), 6.31 (d, *J* = 11.2 Hz), 5.91 (dt, J = 11.2 Hz, *J* = 7.4 Hz, 1 H), 2.24-2.18 (m, 2 H), 1.61-1.58 (m, 2 H), 1.19 (s, 6 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 157.9, 155.5, 149.0, 137.5, 122.8, 116.5, 116.4, 116.0, 115.8, 115.2, 114.9, 71.5, 43.0, 29.4, 24.1. IR 3261, 2970, 1652, 1485, 1434, 1183, 876, 769 cm^{-1}. HRMS $C_{13}H_{17}O_2F$ $(M+Ag)^+$ calcd. 331.0264, obsvd. 331.0280.

Preparation of 95

The same procedure as that of **30** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.20 w/ 20% EtOAc/Hexane, colorless solid. MP = 130-132 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.98-6.95 (m, 1 H), 6.90 (s, 1 H), 6.79 (*d*, *J* = 8.2 Hz, 1 H), 6.35 (d, *J* = 11.2 Hz, 1 H), 5.89 (dt, *J* = 11.2 Hz, *J* = 7.4 Hz, 1 H), 5.2 (bs, 1 H), 2.27 (s, 3 H), 2.24-2.18 (m, 2 H), 1.67-1.57 (m, 2 H), 1.19 (s, 6 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 150.7, 136.6, 130.1, 129.5, 129.3, 123.6, 115.3, 71.3, 43.3, 29.4, 24.1, 20.7. IR 3405, 3085, 2966, 1503, 1421, 1371, 1274, 1202, 1151, 1122, 807, 713 cm^{-1}. HRMS $C_{14}H_{20}O_2$ $(M+Na)^+$ calcd. 243.1361, obsvd. 243.1369.

Preparation of 96

The same procedure as that of **30** was followed**,** Isomeric ratio (*E*/*Z*): 10:1, Major isomer: R_f = 0.30 w/ 33% EtOAc/Hexane, colorless solid. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.83 (d, *J* = 8.7 Hz, 2 H), 6.74 (dd, *J* = 8.7 Hz, *J* = 3.0 Hz, 1 H), 6.66 (d, *J* = 2.9 Hz, 1 H), 6.35 (d, *J* = 11.2 Hz, 1 H), 5.91 (dt, *J* =11.2 Hz, *J* = 7.4 Hz, 1 H), 5.01 (bs, 1 H), 3.77 (s, 3 H), 2.27-2.18 (m, 2 H), 1.64-1.58 (m, 2 H), 1.19 (s, 6 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$): δ 159.8, 154.3, 135.9, 131.1, 123.6, 116.2, 106.5, 101.3, 71.3, 55.9, 43.2, 29.5, 24.2. IR 3410, 3013, 2971, 1604, 1448, 1377, 1261, 1210, 1147, 1131, 904, 784 cm^{-1}. HRMS $C_{14}H_{20}O_3$ $(M+Na)^+$ calcd. 259.1310, obsvd. 259.1320.

Optimization of Reaction Conditions (Table 3.1**)**

See Table 3.1 for more detail.

`Entry 1, Table 3.1

To a 25 mL Schlenk flask equipped with a stir bar were added 3.1 mg $Pd(MeCN)_2Cl_2$ (0.012 mmol, 0.040 equiv.), 2.4 mg of CuCl (0.024 mmol, 0.080 equiv.), 10.0 mg of ^{i}PrQuinox ligand (0.042 mmol, 0.140 equiv.), 12.0 mg of $KHCO_3$ (0.120 mmol, 0.400 equiv.), 2.6 mL of toluene. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 61.9 mg of **30 (**0.300 mmol, 1 equiv.) and 375 μL of *N*-methyl indole (3.00 mmol, 10.0 equiv.) were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for 3 h and diluted with 10 mL of EtOAc. The reaction mixture was pass through a plug of silica gel and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Entry 2, Table 3.1

To a 25 mL Schlenk flask equipped with a stir bar were added 3.1 mg $Pd(MeCN)_2Cl_2$ (0.012 mmol, 0.040 equiv.), 2.4 mg of CuCl (0.024 mmol, 0.080 equiv.), 10.0 mg of ^{i}PrQuinox ligand (0.042 mmol, 0.140 equiv.), 30.0 mg of $KHCO_3$ (0.300 mmol, 1.00 equiv.), 2.6 mL of toluene. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 61.9 mg of **30 (**0.300 mmol, 1 equiv.) and 375 μL of *N*-methyl indole (3.00 mmol, 10.0 equiv.) were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for 3 h and diluted with 10 mL of EtOAc.

The reaction mixture was pass through plug of silica gel and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Entry 3, Table 3.1

To a 25 mL Schlenk flask equipped with a stir bar were added 3.1 mg $Pd(MeCN)_2Cl_2$ (0.012 mmol, 0.040 equiv.), 2.4 mg of CuCl (0.024 mmol, 0.080 equiv.), 10.0 mg of ^{i}PrQuinox ligand (0.042 mmol, 0.140 equiv.), 30.0 mg of $KHCO_3$ (0.300 mmol, 1.00 equiv.), 1.95 mL of toluene and 0.5 mL of THF. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 61.9 mg of **30 (**0.300 mmol, 1 equiv.) and 375 μL of *N*-methyl indole (3.00 mmol, 10.0 equiv.) were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for 3 h and diluted with 10 mL of EtOAc. The reaction mixture was pass through a plug of silica gel and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Entry 4, Table 3.1

The same procedure as that of entry **3** was followed**,**except 5 equiv. of *N*-methyl indole was used.

Entry 5, Table 3.1

The same procedure as that of entry **3** was followed**,** except 15 equiv. of *N*-methyl indole (560 μL) was used.

Scope of Indole Derivatives

General Procedure

To a 25 mL Schlenk flask equipped with a stir bar was added 3.1 mg $Pd(MeCN)_2Cl_2$ (0.012 mmol, 0.040 equiv.), 2.4 mg of CuCl (0.024 mmol, 0.080 equiv.), 10.0 mg of ^{i}PrQuinox ligand (0.042 mmol, 0.140 equiv.), 30.0 mg of $KHCO_3$ (0.300 mmol, 1.000 equiv.), 4.8 mL of toluene and 1.2 mL of THF. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 61.9 mg of **30 (**0.300 mmol, 1 equiv.) and 15.0 equiv. of corresponding indole were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for given time and diluted with 10 mL of EtOAc. The reaction mixture was then pass through silica gel to remove metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Preparation of 67

The same procedure as that of general procedure was followed except 932.8 mg of *N*-Bn-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 58% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = +8.0° (c = 0.18, $CHCl_3$)**,** R_f = 0.52 w/ 20% EtOAC/Hex, colorless solid, M.P. = 64-66 °C (decomposed). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.89 (s, 1 H), 7.35-7.25 (m, 5 H), 7.17-7.10 (m, 5 H), 7.01 (ddd, *J* = 7.9 Hz, *J* = 5.1 Hz, *J* = 1.1 Hz, 2 H), 6.87 (dd, *J* = 7.7 Hz, *J* = 1.7 Hz, 1 H), 6.71 (td, *J* = 7.4 Hz, *J* = 1.3 Hz, 1 H), 5.39-5.30 (m, 2 H), 4.98 (d, *J* = 2.5 Hz, 1 H), 4.84 (td, *J* = 7.2 Hz, *J* = 2.6 Hz, 1 H), 2.19-2.11 (m, 1 H), 1.96-1.87 (m, 1 H), 1.69 (ddd, *J* = 12.2 Hz, *J* = 7.9 Hz, *J* =

6.6 Hz, 1 H), 1.33-1.24 (m, 4 H), 1.17 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.8, 137.9, 136.6, 131.1, 129.0, 128.3, 128.2, 128.1, 127.8, 126.8, 126.6, 122.2, 120.1, 119.1, 119.4, 118.2, 114.2, 109.7, 82.5, 82.4, 50.2, 41.6, 38.7, 28.4, 27.9, 27.4. IR 3211, 2969, 1611, 1482, 1466, 1369, 1811, 1038, 1014, 883, 739 cm^{-1}. HRMS $C_{28}H_{30}NO_2$ $(M+Na)^+$ calcd. 412.2277, obsvd. 412.2281.

Preparation of 68

The same procedure as that of general procedure was followed except 770.0 mg of indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 61% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = +1.0° (c = 0.56, $CHCl_3$)**,** R_f = 0.58 w/ 20% EtOAC/Hex, colorless solid, M.P. = 128-130 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.96 (s, 1 H), 7.38 (dd, J = 8.2 Hz, J = 0.5 Hz, 1 H), 7.32 (dd, J = 8.0 Hz, J = 0.5 Hz, 1 H), 7.26 (s, 1 H), 7.22 (t, *J* = 7.6 Hz, 1 H), 7.18-7.14 (m, 1 H), 7.05-7.02 (m, 2 H), 6.92 (dd, J = 7.7 Hz, J = 1.6 Hz, 1 H), 6.74 (t, *J* = 7.4 Hz, 1 H), 4.99 (d, J = 2.5 Hz, 1 H), 4.89 (td, *J* = 7.2 Hz, *J* = 2.6 Hz, 1 H), 4.04 (qd, J = 15.9 Hz, J = 6.7 Hz, 2 H), 2.27-2.19 (m, 1 H), 2.03-1.94 (m, 1 H), 1.76 (dt, *J* = 12.2 Hz, *J* = 7.3 Hz, 1 H), 1.41-1.34 (m, 4 H), 1.26 (s, 3 H), 0.71-0.67 (m, 2 H), 0.46-0.42 (m, 2 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.8, 136.4, 131.1, 128.3, 128.2, 128.1, 126.0, 121.8, 120.1, 119.9, 119.1, 118.1, 113.4, 109.4, 82.6, 82.5, 50.8, 41.8, 38.7, 28.5, 27.9, 27.5, 11.6, 4.4, 4.3. IR 3211, 2969, 1611, 1482, 1466, 1369, 1811, 1038, 1014, 883, 781 cm^{-1}. HRMS $C_{25}H_{29}NO_2$ $(M+Na)^+$ calcd. 398.2096, obsvd. 398.2107.

Preparation of 69

The same procedure as that of general procedure was followed except 932.8 mg of N-methyl-2-phenyl-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 61%

(average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = -14.0° (c = 0.17, $CHCl_3$), R_f = 0.35 w/ 20% EtOAC/Hex, colorless solid, M.P. = 89-90 °C (decomposed). . ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.77 (s, 1 H), 7.69 (d, *J* = 8.1 Hz, 1 H), 7.45 (bs, 3 H), 7.37 (d, *J* = 8.3 Hz, 2 H), 7.29-7.22 (m, 2 H), 7.14-7.07 (m, 2 H), 6.91 (dd, *J* = 8.0 Hz, *J* = 1.3 Hz, 1 H), 6.72 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1 H), 4.80 (d, *J* = 2.2 Hz, 1 H), 4.61 (td, *J* = 7.4 Hz, *J* = 2.2 Hz, 1 H), 3.56 (s, 3 H), 1.96-1.84 (m, 2 H), 1.64 (ddd, *J* = 12.2 Hz, *J* = 7.9 Hz, *J* = 7.1 Hz, 1 H), 1.49 (ddd, *J* = 12.1 Hz, *J* = 8.7 Hz, *J* = 6.1 Hz, 1 H), 1.20 (s, 3 H), 1.17 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.3, 139.4, 137.5, 131.9, 131.2, 128.7, 128.6, 127.9, 127.8, 127.4, 121.8, 121.4, 119.8, 119.6, 117.4, 112.6, 109.6, 82.3, 81.6, 42.4, 39.1, 31.1, 29.7, 27.9, 27.1. IR 3202, 3056, 2965, 2924, 1729, 1610, 1455, 1367, 1238, 1018, 883, 741 cm^{-1}. HRMS $C_{28}H_{29}NO_2$ $(M+Na)^+$ calcd. 434.2096, obsvd. 434.2087.

Preparation of 70

The same procedure as that of general procedure was followed except 653.4 mg of 1,2-dimethyl-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 70% (average of two run), diastereomeric ratio: >20:1**,** $[\alpha]^{20}_D$ = -25.5° (c = 0.14, $CHCl_3$), R_f = 0.36 w/ 20% EtOAC/Hex, colorless solid, M.P. = . ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.72 (s, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 1 H), 7.12 (td, *J* = 6.9 Hz, *J* = 1.1 Hz, 2 H), 7.08 (qd, *J* = 7.5 Hz, *J* = 1.1 Hz, 1 H), 6.92 (dd, *J* = 8.0 Hz, *J* = 1.3 Hz, 1 H), 6.72 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 4.81 (d, *J* = 2.3 Hz, 1 H), 4.74 (ddd, *J* = 8.5 Hz, *J* = 6.4 Hz, *J* = 2.3 Hz, 1 H), 3.67 (s, 3 H), 2.32 (s, 3 H), 2.27-2.19 (m, 1 H), 2.01-1.91 (m, 1 H), 1.74 (dt, *J* = 12.2 Hz, *J* = 7.8 Hz, 1 H), 1.57-1.50 (m, 1 H), 1.27 (s, 3 H), 1.18 (s, 3H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.2, 136.9, 135.1, 131.1, 128.0, 127.8, 120.7, 119.9,

119.8, 117.5, 110.3, 108.9, 94.7, 82.7, 82.0, 42.3, 39.0, 33.1, 29.9, 28.2, 27.6, 11.3. IR 3303, 2966, 2925, 1659, 1613, 1485, 1366, 1274, 1036, 751 cm^{-1}. HRMS $C_{23}H_{27}NO_2$ $(M+Na)^+$ calcd. 372.1939, obsvd. 372.1953.

Preparation of 71

The same procedure as that of general procedure was followed except 914.8 mg of ethyl-1-methyl-1H-indole-2-carboxylate **(**4.500 mmol, 15.0 equiv.) was added. Yield = 51% (average of two run), diastereomeric ratio: >20:1**,** $[\alpha]^{20}_D$ = -141.0° (c = 0.19, $CHCl_3$), R_f = 0.36 w/ 20% EtOAC/Hex, colorless solid, M.P. = 160-161 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.58 (S, 1 H), 7.85 (dt, *J* = 8.2 Hz, *J* = 0.9 Hz, 1 H), 7.43 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 1 H), 7.31-7.25 (m, 2 H), 7.09 (td, *J* = 8.2 Hz, *J* = 2.0 Hz, 1 H), 7.03 (ddd, *J* = 8.2 Hz, *J* = 6.0 Hz, *J* = 2.0 Hz, 1 H), 6.88 (dd, *J* = 8.1 Hz, *J* = 1.3 Hz, 1 H), 6.83 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1 H), 5.25 (d, *J* = 5.9 Hz, 1 H), 5.03 (apprt. q, *J* = 6.3 Hz, 1 H), 4.56-4.43 (m, 2 H), 3.93 (s, 3 H), 2.23 (ddt, *J* = 12.6 Hz, *J* = 7.8 Hz, *J* = 6.4 Hz, 1 H), 1.86 (ddt, *J* = 12.6 Hz, *J* = 8.6 Hz, *J* = 6.8 Hz, 1 H), 1.73 (ddd, *J* = 12.2 Hz, *J* = 7.8 Hz, *J* = 6.8 Hz, 1 H) 1.61 (ddd, *J* = 12.2 Hz, *J* = 8.6 Hz, *J* = 6.4 Hz, 1 H), 1.46 (t, *J* = 7.1 Hz, 3 H), 1.21 (s, 3 H), 1.04 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 164.3, 155.4, 139.2, 129.8, 127.8, 127.3, 126.6,126.0, 125.1, 123.7, 123.3, 120, 119.8, 117.2, 110.4, 81.9, 80.4, 61.7, 42.8, 38.4, 32.5, 30.9, 28.6, 27.9, 14.4. IR 3333, 2968, 2929, 1672, 1526, 1407, 1382, 1236, 1128, 1015, 739 cm^{-1}. HRMS $C_{25}H_{29}NO_4$ $(M+Na)^+$ calcd. 430.1994, obsvd. 430.1997.

Preparation of 72

The same procedure as that of general procedure was followed except 851.4 mg of methyl 1-methyl-1H-indole-6-carboxylate **(**4.500 mmol, 15.0 equiv.) was added.

Yield = 50% (average of two run), diastereomeric ratio: >20:1**,** $[\alpha]^{20}_{D}$ = -20.2° (c = 0.17, $CHCl_3$), R_f = 0.46 w/ 20% EtOAC/Hex, colorless solid, M.P. = >180 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.87 (s, 1 H), 8.07 (t, *J* = 0.7 Hz, 1 H), 7.69 (dd, *J* = 8.4 Hz, *J* = 1.4 Hz, 1 H), 7.29-7.27 (m, 1 H), 7.24 (s, 1 H), 7.12 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1 H), 6.99 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 6.83 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 1 H), 6.70 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1 H), 4.91 (d, *J* = 2.5 Hz, 1 H), 4.81 (td, *J* = 7.2 Hz, *J* = 2.7 Hz, 1 H), 3.93 (s, 3 H), 3.86 (s, 3 H), 2.22-2.13 (m, 1 H), 1.90 (ddt, *J* = 12.4 Hz, *J* = 8.8 Hz, *J* = 7.3 Hz, 1 H) 1.72 (dt, *J* = 11.9 Hz, *J* = 7.4 Hz, 1 H), 1.37-1.26 (m, 4 H), 1.19 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 168.4, 155.6, 136.3, 131.6, 131.0, 130.6, 128.3, 128.2, 127.9, 123.6, 120.2, 120.1, 119.4, 118.3, 113.9, 111.8, 94.6, 82.6, 82.2, 52.1, 41.8, 38.6, 33.2, 28.5, 27.9, 27.5. IR 3249, 2968, 1709, 1617, 1480, 1370, 1231, 1091, 1039, 889, 770 cm^{-1}. HRMS $C_{24}H_{27}NO_4$ $(M+Na)^+$ calcd. 416.1838, obsvd. 416.1834.

Preparation of 73

The same procedure as that of general procedure was followed except 945.5 mg of 5-bromo-1-methyl-1H-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 62% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_{D}$ = -56.4° (c = 0.56, $CHCl_3$), R_f = 0.4 w/ 20% EtOAC/Hex, colorless solid, M.P. = 140-142 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.87 (S, 1 H), 7.41 (d, *J* = 1.8 Hz, 1 H), 7.26 (dd, *J* = 8.5 Hz, *J* = 2.0 Hz, 1 H), 7.16-7.09 (m, 3 H), 6.98 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 6.85 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 1 H), 6.72 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 1 H), 4.82 (d, *J* = 2.5 Hz, 1 H), 4.78 (td, *J* = 7.2 Hz, *J* = 2.5 Hz, 1 H), 3.82 (s, 3 H), 2.20-2.12 (m, 1 H), 1.88 (ddt, *J* = 12.4 Hz, *J* = 8.8 Hz, *J* = 7.2 Hz, 1 H), 1.71 (ddd, *J* = 12.1 Hz, *J* = 7.8 Hz, *J* = 7.0 Hz, 1 H), 1.31 (m, 4 H), 1.23 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.6, 135.5, 130.9, 129.8, 128.5,

128.3, 127.8, 124.8, 122.1, 120.2, 118.3, 113.0, 112.7, 110.7, 82.6, 82.3, 41.7, 38.6, 33.1, 28.6, 27.9, 27.5, IR 3206, 2968, 2926, 1609, 1581, 1475, 1288, 1263, 1039, 790, 754 cm^{-1}. HRMS $C_{22}H_{34}NBrO_2$ $(M+Na)^+$ calcd. 436.0888, obsvd. 436.0907.

Preparation of 74

The same procedure as that of general procedure was followed except 716.4 mg of 7-ethyl-1-methyl-1H-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 65% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = +25.5° (c = 0.48, $CHCl_3$)**,** R_f = 0.5 w/ 20% EtOAC/Hex, colorless solid, M.P. = 60-62 °C (decomposed). . ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.87 (S, 1 H), 7.15-7.10 (m, 2 H), 7.02-6.87 (m, 5 H), 6.72 (td, *J* = 7.4 Hz, *J* = 1.3 Hz, 1 H), 4.94 (d, *J* = 2.6 Hz, 1 H), 4.85 (td, *J* = 7.2 Hz, *J* = 2.7 Hz, 1 H), 4.06 (s, 3 H), 3.14 (qd, *J* = 7.5 Hz, *J* = 2.9 Hz, 2 H), 2.24-2.16 (m, 1 H), 1.99-1.90 (m, 1 H), 1.74 (ddd, *J* = 12.1 Hz, *J* = 8.0 Hz, *J* = 6.6 Hz, 1 H), 1.39 (t, *J* = 7.5 Hz, 4 H), 1.31 (s, 3 H), 1.24 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.7, 134.9, 131.0, 129.5, 129.1, 128.1,128, 127.7, 122.9, 120.2, 119.5, 118.1, 117.9, 113.2, 82.5, 82.4, 41.4, 38.7, 36.9, 28.4, 27.9, 27.4, 25.6, 16.8, IR 3210, 2967, 1608, 1580, 1451, 1367, 1323, 1037, 870, 753 cm^{-1}. HRMS $C_{24}H_{29}NO_2$ $(M+H)^+$ calcd. 364.2277, obsvd. 364.2294.

Preparation of 75

The same procedure as that of general procedure was followed except 725.4 mg of 5-methoxy-1-methyl-1H-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 57% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = -26.5° (c = 0.60, $CHCl_3$)**,** R_f = 0.58 w/ 20% EtOAC/Hex, colorless solid, M.P. = 138-140 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.83 (s, 1 H), 7.18 (d, *J* = 8.8 Hz, 1 H), 7.13-7.09 (m, 1 H), 7.02 (s, 1 H), 6.98 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 6.87 (td, *J* = 8.1 Hz, *J* = 2.1 Hz, 1 H), 6.71 (td, *J* = 7.4

Hz, *J* = 1.2 Hz, 1 H), 6.65 (d, *J* = 2.4 Hz, 1 H), 4.89 (d, *J* = 2.6 Hz, 1 H), 4.83 (td, *J* = 7.2 Hz, *J* = 2.8 Hz, 1 H), 3.78 (s, 3 H), 3.70 (s, 3 H), 2.18 (ddt, *J* = 12.7 Hz, *J* = 7.9 Hz, *J* = 6.5 Hz, 1 H), 1.93 (ddt, *J* = 12.5 Hz, *J* = 8.9 Hz, *J* = 7.1 Hz, 1 H) 1.72 (ddd, *J* = 12.2 Hz, *J* = 8.0 Hz, *J* = 6.7 Hz, 1 H), 1.37-1.29 (m, 4 H), 1.21 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.8, 153.9, 133.3, 131.1, 128.3, 128.1, 127.9, 127.8, 120.1, 118.1, 112.8, 112.2, 109.9, 101.7, 94.6, 82.5, 82.4, 56.1, 41.5, 41.5, 38.7, 33.2, 28.4, 27.9, 27.4. IR 3207, 2965, 2831, 1622, 1579, 1489, 1369, 1270, 1174, 1035, 1015, 798, 755 cm^{-1}. HRMS $C_{23}H_{27}NO_3$ $(M+Na)^+$ calcd. 388.1889, obsvd. 388.1894.

Preparation of 76

To a 25 mL Schlenk flask equipped with a stir bar were added 3.1 mg $Pd(MeCN)_2Cl_2$ (0.012 mmol, 0.040 equiv.), 2.4 mg of CuCl (0.024 mmol, 0.080 equiv.), 10.0 mg of ^{i}PrQuinox ligand (0.300 mmol, 0.140 equiv.), 30.0 mg of $KHCO_3$ (0.300 mmol, 1.000 equiv.), 2.0 mL of toluene and 0.5 mL of THF. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 61.9 mg of **30 (**0.300 mmol, 1 equiv.) and 400 μL of N-methylpyrrole (4.50 mmol, 15.0 equiv.) were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for 3 h **in the dark** and diluted with 10 mL of EtOAc. The reaction mixture was pass through silica gel to remove metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography. Yield = 53% (average of two run), diastereomeric ratio = 20:1, $[\alpha]^{20}_D$ = +47.4° (c = 0.34, $CHCl_3$)**,** R_f = 0.6 w/ 20% EtOAC/Hex, colorless solid, M.P. = 94-96 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.54 (s,

1 H), 7.13 (td, *J* = 7.6 Hz, *J* = 1.5 Hz, 1 H), 6.97 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 6.77 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 6.59 (dd, *J* = 2.5 Hz, *J* = 1.8 Hz, 1 H), 6.13 (dd, *J* = 3.5 Hz, *J* = 2.8 Hz, 1 H), 6.04 (ddd, *J* = 3.7 Hz, *J* = 1.9 Hz, *J* = 1.2 Hz, 1 H), 4.83 (td, *J* = 7.1 Hz, *J* = 2.8 Hz, 1 H), 4.74 (d, *J* = 2.7 Hz, 1 H), 3.14 (s, 3 H), 2.23 (dq, *J* = 12.7 Hz, *J* = 7.6 Hz, 1 H), 1.86 (dddd, *J* = 12.7 Hz, *J* = 9.1 Hz, *J* = 6.9 Hz, *J* = 5.7 Hz, 1 H), 1.69 (ddd, *J* = 12.2 Hz, *J* = 8.1 Hz, *J* = 5.7 Hz, 1 H) 1.28-1.24 (m, 4 H), 1.20 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.7, 131.1, 130.3, 128.3, 126.4, 122.2, 120.6, 118.1, 107.6, 106.5, 82.0, 81.9, 41.1, 38.7, 33.9, 27.7, 27.6, 26.9. IR 3248, 2969, 2928, 1582, 1483, 1302, 1232, 1037, 1013, 877, 757 cm^{-1}. HRMS $C_{18}H_{23}NO_2$ $(M+Na)^+$ calcd. 308.1626, obsvd. 308.1628.

Substrate Scope (Table 3.3)

General Procedure

To a 25 mL Schlenk flask equipped with a stir bar were added 3.1 mg $Pd(MeCN)_2Cl_2$ (0.012 mmol, 0.040 equiv.), 2.4 mg of CuCl (0.024 mmol, 0.080 equiv.), 10.0 mg of ^{i}PrQuinox ligand (0.042 mmol, 0.140 equiv.), 30.0 mg of $KHCO_3$ (0.300 mmol, 1.000 equiv.), 1.95 mL of toluene and 0.5 mL of THF. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 61.9 mg of **30 (**0.300 mmol, 1 equiv.) and 560 μL of N-methyl indole (4.50 mmol, 15.0 equiv.) were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for 3 h and diluted with 10 mL of EtOAc. The reaction mixture was then pass through silica gel to remove

metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Preparation of 77

The same procedure as that of general procedure was followed. Yield = 81% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = +7.2° (c = 0.31, $CHCl_3$) R_f = 0.66 w/ 33% EtOAC/Hex, colorless solid, M.P. = 108-110 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.88 (s, 1 H), 7.30 (dd, *J* = 8.2 Hz, *J* = 0.7 Hz, 1 H), 7.25 (d, *J* = 7.9 Hz, 1 H), 7.20 (td, *J* = 7.6 Hz, *J* = 1.0 Hz, 1 H), 7.11 (td, *J* = 7.6 Hz, *J* = 1.5 Hz, 1 H), 7.05 (s, 1 H), 7.00 (td, *J* = 8.2 Hz, *J* = 0.9 Hz, 2 H), 6.85 (dd, *J* = 7.7 Hz, *J* = 1.5 Hz, 1 H), 4.95 (d, *J* = 2.6 Hz, 1 H), 4.84 (td, *J* = 7.2 Hz, *J* = 2.7 Hz, 1 H), 3.82 (s, 3 H), 2.23-2.16 (m, 1 H), 1.93 (ddt, *J* = 12.5 Hz, *J* = 8.9 Hz, *J* = 7.1 Hz, 1 H), 1.72 (ddd, *J* = 12.2 Hz, *J* = 7.9 Hz, *J* = 6.7 Hz, 1 H), 1.34-1.28 (s, 4 H), 1.21 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.7, 136.9, 131.1, 128.1, 127.9, 127.2, 121.9, 120.1, 119.6, 119.1, 118.1, 113.3, 109.2, 82.4, 41.4, 38.6, 33.0, 28.3, 27.9, 27.4. IR 3209, 2967, 2925, 1612, 1581, 1482, 1369, 1269, 1229, 1038, 1012, 883 cm^{-1}. HRMS $C_{22}H_{25}NO_2$ $(M+Na)^+$ calcd. 358.1783, obsvd. 358.1787.

Preparation of 78

The same procedure as that of general procedure was followed except 82.3 mg of **92 (**0.300 mmol, 1 equiv.) was added. Yield = 87% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = -10.0° (c = 0.24, $CHCl_3$), R_f = 0.35 w/ 20% EtOAC/Hex, colorless solid, M.P. = 102-104 °C (decomposed). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.53 (s, 1 H), 7.4 (dd, J = 8.4 Hz, J = 2.2 Hz, 1 H), 7.33 (ddd, J = 8.4 Hz, J = 7.4 Hz, J = 0.8 Hz, 1 H), 7.25 (ddd, J = 8.2 Hz, J = 7.0 Hz, J = 1.1 Hz, 1 H), 7.20 (d, *J* = 2.2 Hz, 1 H), 7.12 (s, 1

H), 7.08-7.04 (m, 2 H), 4.94 (d, *J* = 2.5 Hz, 1 H), 4.82 (ddd, *J* = 7.8 Hz, *J* = 6.9 Hz, *J* = 2.5 Hz, 1 H), 3.82 (s, 3 H), 2.22 (dddd, *J* = 12.5 Hz, *J* = 7.9 Hz, *J* = 6.7 Hz, *J* = 5.8 Hz, 1 H), 1.89 (dddd, *J* = 12.4 Hz, *J* = 8.8 Hz, *J* = 7.8 Hz, *J* = 7.2 Hz, 1 H), 1.77 (dt, *J* = 12.2 Hz, *J* = 7.5 Hz, 1 H), 1.44-1.37 (m, 1 H), 1.32 (s, 3 H), 1.22 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 158.8, 136.9, 128.8, (128.3, 128.2, 128.2, CF_3), 127.8, 127.4, 125.5, 122.1, 119.4, 119.3, 118.5, 112.1, 109.4, 82.9, 82.3, 41.9, 38.6, 33.1, 29.9, 28.6, 27.9, 27.5. IR 2966, 2924, 1614, 1466, 1324, 1279, 1108, 1074, 739 cm^{-1}. HRMS $C_{23}H_{24}O_2F_3$ $(M+Na)^+$ calcd. 404.1838, obsvd. 404.1843.

Preparation of 94

The same procedure as that of general procedure was followed except 72.4 mg of **4.S13** (0.300 mmol, 1 equiv.) was added. Yield = 87% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = -10.0° (c = 0.24, $CHCl_3$), R_f = 0.52 w/ 20% EtOAC/Hex, colorless solid, M.P. = 98-100 °C (decomposed). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.90 (s, 1 H), 7.33-7.20 (m, 3 H), 7.08-7.01 (m, 2 H), 6.92 (d, *J* = 8.5 Hz, 1 H), 6.82 (d, *J* = 2.6 Hz, 1 H), 4.94 (d, *J* = 2.6 Hz, 1 H), 4.79 (td, *J* = 7.3 Hz, *J* = 2.6 Hz, 1 H), 3.82 (s, 3 H), 2.20 (ddt, *J* = 12.6 Hz, *J* = 7.9 Hz, *J* = 6.5 Hz, 1 H), 1.96-1.88 (m, 1 H), 1.74 (ddd, *J* = 12.2 Hz, *J* = 7.9 Hz, *J* = 6.7 Hz, 1 H), 1.40-1.28 (m, 4 H), 1.20 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.5, 136.9, 130.5, 130.0, 128.0, 127.7, 127.2, 124.8, 122.1, 119.5, 119.4, 119.3, 112.5, 109.3, 82.5, 82.4, 41.2, 38.7, 33.1, 28.3, 27.9, 27.4. IR 3204, 2969, 2927, 1719, 1475, 1370 1264, 1014, 877, 738 cm^{-1}. HRMS $C_{22}H_{24}NO_2Cl$ $(M+K)^+$ calcd. 408.1133, obsvd. 408.1140.

Preparation of 80

To a 25 mL Schlenk flask equipped with a stir bar were added 2.6 mg $Pd(MeCN)_2Cl_2$ (0.010 mmol, 0.040 equiv.), 2.0 mg of CuCl (0.020 mmol, 0.080 equiv.), 8.4 mg of ^{i}PrQuinox ligand (0.035 mmol, 0.140 equiv.), 25.0 mg of $KHCO_3$ (0.250 mmol, 1.000 equiv.), 1.6 mL of toluene and 0.4 mL of THF. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 56.0 mg of **93 (**0.250 mmol, 1 equiv.) and 470 μL of *N*-methyl indole (3.75 mmol, 15.0 equiv.) were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for 3 h and diluted with 10 mL of EtOAc. The reaction mixture was then pass through silica gel to remove metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Yield = 78% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_{D}$ = +39.3° (c = 0.45, $CHCl_3$), R_f = 0.55 w/ 20% EtOAC/Hex, colorless liquid, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.59 (s, 1 H), 7.30 (d, *J* = 8.0 Hz, 1 H), 7.21 (t, *J* = 8.4 Hz, 2 H), 7.03-6.98 (m, 2 H), 6.92 (dd, *J* = 8.8 Hz, *J* = 5.0 Hz 1 H), 6.78 (td, *J* = 8.3 Hz, *J* = 3.1 Hz, 1 H), 6.53 (dd, *J* = 9.9 Hz, *J* = 3.1 Hz, 1 H), 4.98 (d, *J* = 2.7 Hz, 1 H), 4.82 (td, *J* = 7.2 Hz, *J* = 2.7 Hz, 1 H), 3.82 (s, 3 H), 2.25-2.16 (m, 1 H), 1.91 (dddd, *J* = 12.5 Hz, *J* = 8.9 Hz, *J* = 7.3 Hz, *J* = 6.6 Hz, 1 H), 1.73 (ddd, *J* = 12.2 Hz, *J* = 8.0 Hz, *J* = 6.5 Hz, 1 H) 1.35-1.28 (m, 4 H), 1.19 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 158.1, 151.8, 137.0, 129.7, 129.6, 127.1, 122.2, 119.7, 119.3, 118.9, 118.8, 117.2, 116.9, 114.5, 114.3, 112.8, 109.3, 82.5, 82.4, 40.9, 38.7, 33.0, 28.1, 27.8, 27.3. IR 3242, 2970, 1716, 1486, 1372,

1233, 1184, 877, 761 cm^{-1}. HRMS $C_{22}H_{24}NO_2F$ $(M+Na)^+$ calcd. 376.1689, obsvd. 376.1683.

Preparation of 81

The same procedure as that of general procedure was followed except 66.1 mg of 95 **(**0.300 mmol, 1 equiv.) was added. Yield = 58% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = -8.2° (c = 0.36, $CHCl_3$), R_f = 0.44 w/ 20% EtOAC/Hex, colorless solid, M.P. = 109-111 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.75 (s, 1 H), 7.35 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.2 Hz, 1 H), 7.22 (ddd, *J* = 8.1 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz, 1 H), 7.11 (s, 1 H), 7.04 (ddd, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.0 Hz, 1 H), 6.93 (dd, *J* = 8.1 Hz, *J* = 2.0 Hz, 1 H), 6.89 (d, *J* = 8.0 Hz, 1 H), 6.72 (d, *J* = 1.5 Hz, 1 H), 4.88 (d, *J* = 2.6 Hz, 1 H), 4.80 (td, *J* = 7.2 Hz, *J* = 2.6 Hz, 1 H), 3.81 (s, 3 H), 2.22-2.12 (m, 4 H), 1.94 (ddt, *J* = 12.4 Hz, *J* = 8.9 Hz, *J* = 7.3 Hz, 1 H), 1.72 (ddd, *J* = 12.1 Hz, *J* = 7.8 Hz, *J* = 7.1 Hz, 1 H) 1.40-1.34 (m, 1 H), 1.30 (s, 3 H), 1.21 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.3, 136.9, 131.4, 129.0, 128.7, 128.0, 127.4, 121.9, 119.7, 119.1, 117.9, 113.4, 109.2, 82.6, 82.5, 41.9, 38.7, 33.1, 28.7, 28.1, 27.6, 20.8. IR 3237, 2967, 2926, 1613, 1492, 1423, 1326, 1263, 1038, 880, 747 cm^{-1}. HRMS $C_{23}H_{27}O_2N$ $(M+Na)^+$ calcd. 372.1939, obsvd. 372.1944.

Preparation of 82

The same procedure as that of general procedure was followed except 70.1 mg of **96 (**0.300 mmol, 1 equiv.) was added. Yield = 44% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = +18.2° (c = 0.52, $CHCl_3$), R_f = 0.41 w/ 20% EtOAC/Hex, colorless solid, M.P. = 85-88 °C (decomposed). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.40 (s, 1 H), 7.30-7.27 (m, 2 H), 7.19 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1 H), 7.03-7.00 (m, 2 H), 6.92 (d, *J* =

8.7 Hz, 1 H), 6.67 (dd, *J* = 8.7 Hz, *J* = 3.1 Hz, 1 H), 6.45 (d, *J* = 3.1 Hz, 1 H), 4.95 (d, *J* = 2.7 Hz, 1 H), 4.81 (td, *J* = 7.2 Hz, *J* = 2.7 Hz, 1 H), 3.81 (s, 3 H), 3.59 (s, 3 H), 2.22-2.14 (m, 1 H), 1.95 (ddt, *J* = 12.5 Hz, *J* = 8.9 Hz, *J* = 7.0 Hz, 1 H) 1.71 (ddd, *J* = 12.2 Hz, *J* = 8.0 Hz, *J* = 6.7 Hz, 1 H), 1.36-1.28 (m, 4 H), 1.20 (s, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 153.2, 149.7, 136.9, 129.3, 127.9, 127.1, 121.9, 119.8, 119.2, 118.4, 117.4, 113.2, 112.2, 109.1, 82.5, 82.3, 55.7, 41.3, 38.7, 33.0, 28.3, 27.9, 27.4. IR 3247, 2966, 2926, 1613, 1488, 1465, 1369, 1262, 1040, 878, 775 cm^{-1}. HRMS $C_{23}H_{27}NO_3$ $(M+Na)^+$ calcd. 388.1889, obsvd. 388.1893.

Preparation of 83

To a 250 mL Schlenk flask equipped with a stir bar were added 15.6 mg $Pd(MeCN)_2Cl_2$ (0.06 mmol, 0.040 equiv.), 11.9 mg of CuCl (0.12 mmol, 0.080 equiv.), 50.5 mg of ^{i}PrQuinox ligand (0.210 mmol, 0.140 equiv.), 150.0 mg of $KHCO_3$ (1.50 mmol, 1.00 equiv.), 9.7 mL of toluene and 2.4 mL of THF. A three-way joint fitted with a balloon of O_2 was attached and the flask was evacuated and refilled with O_2 three times. The mixture was stirred for 20 min at room temperature under an atmosphere of O_2. To the reaction mixture, 267.0 mg of **31 (**1.500 mmol, 1.00 equiv.) and 2.81 mL of N-methyl indole (22.5 mmol, 15.0 equiv.) were added and the flask was evacuated and refilled with O_2 three more times. The reaction mixture was stirred for 5 h and diluted with 50 mL of EtOAc. The reaction mixture was then pass through silica gel to remove metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Yield = 82% (average of two run, *Note: 2.56 g of N-methyl indole was recovered*), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = +4.0° (c = 0.56, $CHCl_3$), R_f = 0.5 w/ 33%

EtOAC/Hex, colorless solid, M.P. = 148-150 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.79 (s, 1 H), 7.32-7.27 (m, 2 H), 7.21 (ddd, *J* = 8.2 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz, 1 H), 7.12 (td, *J* = 7.6 Hz, *J* = 1.4 Hz, 1 H), 7.07 (s, 1 H), 7.04-7.01 (m, 1 H), 7.00-6.97 (m, 1 H), 6.89 (dd, *J* = 7.7 Hz, *J* = 1.7 Hz, 1 H), 6.71 (td, *J* = 7.4 Hz, *J* = 1.3 Hz, 1 H), 4.98 (d, *J* = 2.85 Hz, 1 H), 4.77 (td, *J* = 7.3 Hz, *J* = 2.9 Hz, 1 H), 3.92-3.78 (m, 5 H), 2.19-2.1 (m, 1 H), 1.93-1.83 (m, 2 H), 1.62-1.54 (m, 1 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.7, 137.1, 131.1, 128.2, 128.0, 127.9, 127.8, 127.1, 122, 120.2, 119.8, 119.2, 113.3, 109.2, 83.5, 68.6, 41.9, 33.0, 28.3, 26.4. IR 3303, 2932, 2867, 1650, 1603, 1455, 1357, 1251, 1093, 1054, 976, 781 cm^{-1}. HRMS $C_{20}H_{21}NO_2$ $(M+K)^+$ calcd. 346.1209, obsvd. 346.1219

Preparation of 84

The same procedure as that of general procedure was followed except 57.7 mg of **36 (**0.300 mmol, 1 equiv.) was added. Yield = 62% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_D$ = -43.0° (c = 0.13, $CHCl_3$), R_f = 0.33 w/ 20% EtOAC/Hex, colorless solid, M.P. = 140-141 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 9.16 (S, 1 H), 7.41 (dt, *J* = 8.0 Hz, *J* = 0.92 Hz, 1 H), 7.3 (dt, *J* = 8.2 Hz, *J* = 0.9 Hz, 1 H), 7.21 (ddd, *J* = 8.2 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz, 1 H), 7.16-7.11 (m, 1 H), 7.09-7.04 (m, 2 H), 6.95 (dd, *J* = 8.0 Hz, *J* = 1.3 Hz, 1 H), 6.76 (td, *J* = 7.4 Hz, *J* = 1.3 Hz, 1 H), 4.52 (d, *J* = 2.0 Hz, 1 H), 4.24-4.23 (m, 2 H), 3.79 (s, 3 H), 3.69-3.62 (m, 2 H), 1.88-1.77 (m, 2 H), 1.61-1.53 (m, 4 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.4, 136.7, 131.3, 129.4, 128.4, 128.3,127.5, 121.6, 119.9, 119.4, 119.1, 118.1, 112.5, 109.3, 82.7, 69.4, 46.3, 33, 29.7, 25.6, 23.5. IR 3049, 2933, 2854, 1612, 1454, 1374, 1264, 1173, 1081, 937, 907, 736 cm^{-1}. HRMS $C_{21}H_{23}NO_2$ $(M+Na)^+$ calcd. 344.1626, obsvd. 344.1629.

Preparation of 85

The same procedure as that of general procedure was followed except 58.0 mg of **39 (**0.300 mmol, 1 equiv.) was added. Yield = 30% (average of two run), diastereomeric ratio: >20:1, $[\alpha]^{20}_{D}$ = -26.0° (c = 0.78, $CHCl_3$), R_f = 0.45 w/ 50% EtOAC/Hex, colorless oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.86 (s, 1 H), 7.26-7.24 (m, 2 H), 7.22 (s, 1 H), 7.22-7.17 (m, 1 H), 7.14-7.09 (m, 1 H), 7.03-6.99 (m, 2 H), 6.91 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 1 H), 6.75 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 4.58 (d, *J* = 3.4 Hz, 1 H), 4.39 (dt, *J* = 10.1 Hz, *J* = 2.9 Hz, 1 H), 4.00-3.88 (m, 3 H), 3.79 (s, 3 H), 3.72 (dd, *J* = 11.8 Hz, *J* = 2.3 Hz, 1 H), 3.59 (dt, *J* = 11.3 Hz, *J* = 5.7 Hz, 1 H), 3.47 (dd, *J* = 11.8 Hz, *J* = 10.1 Hz, 1 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.8, 136.9, 130.7, 128.4, 127.9, 127.3, 121.9, 120.5, 119.4, 119.3, 117.8, 112.2, 109.3, 79.4, 69.8, 67.6, 66.3, 41.6, 33.0. IR 3049, 2933, 2854, 1612, 1454, 1374, 1264, 1173, 1081, 937, 907, 736 cm^{-1}. HRMS $C_{20}H_{21}NO_3$ $(M+Na)^+$ calcd. 346.1419, obsvd. 346.1429.

Product Derivatization

Synthesis of 86

In a dry round bottom flask 89 mg (0.29 mmol, 1.0 equiv.) of **83** was dissolved in 2.9 mL of DCM. To this 80 mg (0.32 mmol, 1.1 equiv.) of PPTS was added and the reaction mixture was cooled to -78 °C. At this temperature solution of 57 mg (0.32 mmol, 1.1 equiv.) of NBS in 2.9 mL of THF was added dropwise. The reaction mixture was allowed to stir for 15 min at -78 °C and quenched with 2 mL of $NaHCO_3$. The organic phase was diluted with 5 mL of DCM and washed with water (10 mL X 2) followed by brine (10 mL) wash. The organic layer was dried on Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by silica gel column

chromatography with 2% to 10% EtOAc:Hex as eluent to give the desired product in 92% yield. Yield = 92% (average of two run), $[\alpha]^{20}_{D}$ = +140.3° (c = 0.39, $CHCl_3$), R_f = 0.66 w/ 20% EtOAC/Hex, colorless solid, M.P. = 114-120 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.66-7.63 (m, 1 H), 7.59-7.56 (m, 1 H), 7.33-7.25 (m, 2 H), 7.21-7.11 (m, 4 H), 4.77 (d, *J* = 3.5 Hz, 1 H), 4.57 (td, *J* = 6.8 Hz, *J* = 3.6 Hz, 1 H), 3.74 (m, 5 H), 1.65-1.57 (m, 2 H), 1.40-1.30 (m, 2 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 152.7, 146.1, 133.9, 132.1, 127.9, 125.2, 123.8, 121.8, 120.1, 120.0, 119.9, 117.8, 116.7, 108.7, 86.9, 82.6, 68.9, 39.0, 38.9, 30.0, 28.0, 27.4, 26.1. IR 2929, 2866, 1638, 1602, 1419, 1380, 1233, 1064, 735 cm^{-1}. HRMS $C_{20}H_{19}O_2N$ $(M+Na)^+$ calcd. 306.1494, obsvd. 309.1503.

Synthesis of 87

In a dry round bottom flask 80 mg (0.26 mmol, 1.0 equiv.) of **1g** was dissolved in 2.6 mL of DCM. The reaction mixture was cooled to -78 °C, at this temperature 4.8 mL of DMDO in acetone (0.78 mmol, 3.0 equiv.) was added dropwise. The reaction mixture was allow to stir for 2h (till completion) at -78 °C and quench with 2 mL of water. The organic phase was diluted with 5 mL of DCM and washed with water (10 mL X 2) followed by brine (10 mL) wash. The organic layer was dried on Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with 5% to 50% EtOAc:Hex as eluent to give the desired product in 73% yield. Yield = 73% (average of two run), Diastereomeric ratio: 1:1, *Note: two diastereomers were readily separated by column chromatography (5% EtOAc:Hex to 50% EtOAc:Hex).*

Separation conditions for enantiomers are shown in Table 3.4 and Table 3.5.

Table 3.4. Separation conditions for determination of enantiopurity (for substrates)

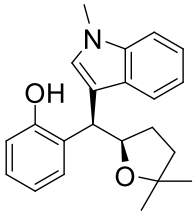
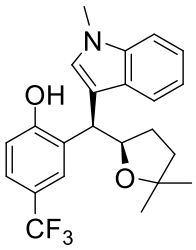
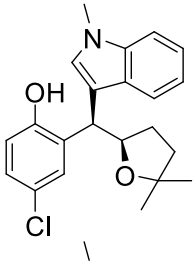
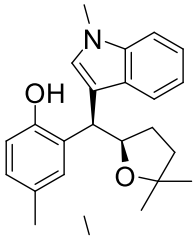
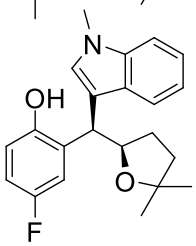
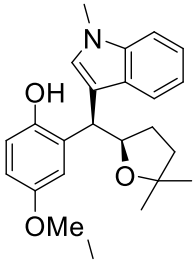
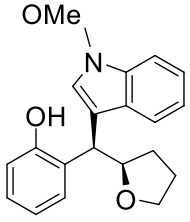
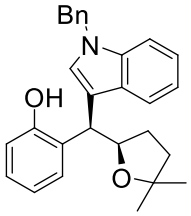
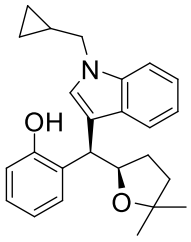
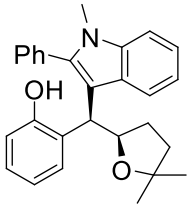
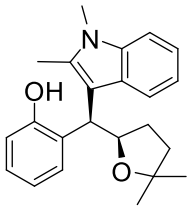
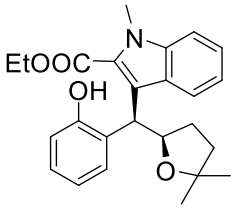
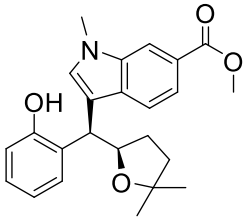
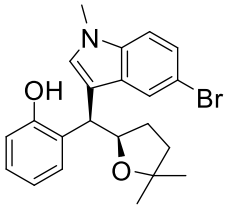
Compound	Conditions	Retention time	er
	SFC, 5% Methanol, 3 mL/min, Whelko chiral column	9.80 and 10.54 min	97:3
	SFC, 5% Methanol, 3 mL/min, OD-H chiral column	9.80 and 10.54 min	95.5:4.5
	SFC, 3% Methanol, 3 mL/min, Whelko chiral column	13.26 and 14.26 min	97:3
	SFC, 5% Methanol, 3 mL/min, AD-H chiral column	5.09 and 5.80 min	95.5:4.5
	SFC, 1% Methanol, 4 mL/min, Whelko column	20.86 and 23.37 min	94.5:5.5
	SFC, 7% Methanol, 3 mL/min, Whelko chiral column	10.66 and 11.60 min	95.5:4.5
	SFC, 5% Methanol, 3 mL/min, AD-H chiral column	11.31 and 12.13 min	97:3

Table 3.5. Separation conditions for determination of enantiopurity (for nucleophiles)

Compound	Conditions	Retention time	er
	SFC, 5% Methanol, 3 mL/min, AD-H chiral column	8.26 and 10.58 min	97:3
	SFC, 3% Methanol, 3 mL/min, OJ-H chiral column	9.99 and 17.77 min	98.5:1.5
	SFC, 3% Methanol, 3 mL/min, OJ-H chiral column	7.41 and 8.42 min	98.5:1.5
	SFC, 3% Methanol, 3 mL/min, OJ-H chiral column	7.53 and 8.67 min	98.5:1.5
	SFC, 5% Methanol, 3 mL/min, AD-H chiral column	6.61 and 8.81 min	98.5:1.5
	SFC, 5% Methanol, 3 mL/min, OJ-H chiral column	11.25 and 12.48 min	98:2
	SFC, 10% Methanol, 3 mL/min, OD-H chiral column	6.98 and 8.82 min	98:2

Diastereomer 1

$[\alpha]^{20}_{D}$ = +114.5° (c = 1.05, $CHCl_3$), R_f = 0.5 w/ 20% EtOAC/Hex, colorless liquid, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.42 (dd, *J* = 7.4 Hz, *J* = 1.2 Hz, 1 H), 7.13-7.09 (m, 1 H), 7.02-6.96 (m, 2 H), 6.87 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 6.80 (dd, *J* = 7.6 Hz, *J* = 1.2 Hz, 1 H), 6.58 (td, *J* = 7.4 Hz, *J* = 0.9 Hz, 1 H), 6.16 (d, *J* = 7.8 Hz, 1 H), 5.70 (s, 1 H), 5.49 (s, 1 H), 4.82 (dt, *J* = 10.6 Hz, *J* = 6.6 Hz, 1 H), 4.19 (dt, *J* = 8.3 Hz, *J* = 6.3 Hz, 1 H), 4.01-3.97 (m, 1 H) 3.20 (d, *J* = 10.59, 1 H), 2.88 (s, 3 H), 2.52 (dq, *J* = 12.5 Hz, *J* = 7.2 Hz, 1 H), 2.09 (dt, *J* = 13.8 Hz, *J* = 7.0 Hz, 2 H), 1.90-1.81 (m, 1 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.7, 151.5, 129.6, 128.9, 127.7, 127.4, 125.5, 125.1, 123.0, 118.1, 103.9, 86.0, 78.4, 68.7, 48.0, 32.8, 30.6, 26.1. IR 3354, 2928, 2875, 1611, 1456, 1374, 741 cm^{-1}. HRMS $C_{20}H_{21}O_3N$ $(M+Na)^+$ calcd. 346.1419, obsvd. 346.1425.

Diastereomer 2

$[\alpha]^{20}_{D}$ = +14.7° (c = 0.90, $CHCl_3$), R_f = 0.3 w/ 20% EtOAC/Hex, colorless liquid, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.09 (dd, *J* = 7.4 Hz, *J* = 0.9 Hz, 1 H), 7.03-6.96 (m, 2 H), 6.87 (dd, *J* = 7.4 Hz, *J* = 1.6 Hz, 1 H), 6.83-6.81 (m, 1 H), 6.76 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 1 H), 6.57 (td, *J* = 7.4 Hz, *J* = 0.9 Hz, 1 H), 6.35 (s, 1 H), 6.23 (d, *J* = 7.83 Hz, 1 H), 5.58 (s, 1 H), 4.54 (ddd, *J* = 9.8 Hz, *J* = 7.8 Hz, *J* = 6.3 Hz, 1 H), 4.15-4.09 (m, 1 H), 3.98 (td, *J* = 8.1 Hz, *J* = 5.3 Hz, 1 H), 3.29 (d, *J* = 9.8 Hz, 1 H), 2.98 (s, 3 H), 2.04 (m, 2 H), 1.90-1.71 (m, 2 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.1, 151.1, 131.3, 129.7, 129.3, 128.4, 126.9, 122.8, 123.6, 118.2, 117.9, 105.4, 101.4, 83.4, 80.9, 69.2, 50.3, 32.4, 30.2, 24.8. IR 3354, 2928, 2875, 1611, 1456, 1374, 741 cm^{-1}. HRMS $C_{20}H_{21}O_3N$ $(M+Na)^+$ calcd. 346.1419, obsvd. 346.1424.

Biological Experimentals

Materials

The following reagents were obtained from commercial sources as indicated: DMEM/F12 containing 2.5 mM L-glutamine and 15 mM HEPES buffer (HyClone); fetal bovine serum (FBS) was heat inactivated (HyClone); 100x insulin-transferrin-selenium-X (Gibco); 100x penicillin-streptomycin-glutamine (PS) (Gibco); Human Epidermal Growth Factor (EGF), Recombinant (BD Biosciences); Molecular biology grade DMSO (Sigma); 5-Bromo-2'-deoxyuridine (BrdU) (Sigma); 0.05% Trypsin-EDTA (Gibco); Bovine serum albumin (BSA) fraction V (EMD); Absolute Reagent Alcohol (EtOH) (Mallinckrodt); Concentrated HCl (Sigma); Sodium tetraborate decahydrate (Sigma); Triton X-100 (Sigma); Tween-20 (Bio-Rad); Hanks' balanced salt solution (HBSS) with calcium chloride and magnesium chloride (Gibco); G3G4 mouse anti-BrdU concentrate (Developmental Studies Hybridoma Bank at the University of Iowa); Alexa Fluor-488 goat anti-mouse IgG (Invitrogen); and Propidium Iodide (Calbiochem).

Initial Evaluation of Compounds 67-87

MCF-7 (Luminal ER+) cells were seeded at 3,500 cells per well in a 96 well flat bottom plate with DMEM/F12 media supplemented with 10% FBS, 1x ITS-X, 1x PS, 2.5 nM EGF and incubated with 5% CO_2 at 37 °C overnight. The compounds **67-87**, were dissolved in molecular biology grade DMSO to achieve a 10 mM stock. The 10 mM DMSO stock solutions were subsequently diluted to a final concentration of 10 μM using DMEM/F12 media supplemented with 2% FBS, 1x ITS-X, 1x PS, 2.5 nM EGF. The media was aspirated from the 96 well plate containing the MCF-7 cells and the media containing the compounds or DMSO vehicle controls were added. After culturing for 3

days, cell proliferation was measured by metabolic reduction of MTS [(3 - (4,5 – dimethylthiazol - 2-yl) – 5 - (3 - carboxymethoxyphenyl) - 2 - (4 - sulfophenyl) - 2H - tetrazolium, inner salt)]. This assay was performed using the CellTiter 96 AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). The absorbance values were normalized to the DMSO vehicle controls.

Dose Response of Compounds (±)-69, (+)-69, (–)-69, (±)-72, (+)-72, and (–)-72

MCF-7 (Luminal ER+) cells were seeded at 1,500 cells per well and MCF-10A (normal breast) cells were seeded at 9,000 cells per well in a 96 well flat bottom plate with DMEM/F12 media supplemented with 10% FBS, 1x ITS-X, 1x PS, 2.5 nM EGF and incubated with 5% CO_2 at 37 °C overnight. The compounds **(±)-69, (+)-69, (–)-69, (±)-72, (+)-72,** and **(–)-72**, were dissolved in molecular biology grade DMSO to achieve a 30 mM stock. The 30 mM DMSO stock solutions were subsequently diluted using DMEM/F12 media supplemented with 2% FBS, 1x ITS-X, 1x PS, 2.5 nM EGF to achieve 12 different concentrations using an automated liquid handler (EP Motion 5075, Eppendorf). Additionally, the corresponding DMSO vehicle controls for each concentration were diluted using the same media. The media was aspirated from the 96 well plate containing the cells and the media containing the different dilutions of compounds and DMSO vehicle controls were added (day 0). The cells were also treated on days 2 and 4 by aspirating the media and adding fresh media containing the compounds and DMSO vehicle controls. On day 5 of treatment, the MTS assay was performed using the CellTiter 96 AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). The absorbance values were normalized to the DMSO vehicle controls

corresponding to each concentration. The normalized values were plotted as an average ± standard deviation of 4 wells per condition and these data were analyzed using the dose response nonlinear curve fitting function with Origin 8.0.

BrdU/PI Cell Cycle Analysis of (±)-69 and (±)-72

MCF-7 (Luminal ER+) cells were seeded at 150,000 cells per well in a 6 well flat bottom plate with DMEM/F12 media supplemented with 10% FBS, 1x ITS-X, 1x PS, 2.5 nM EGF and incubated with 5% CO_2 at 37 °C overnight. The 30 mM DMSO stock solutions of compounds **(±)-69** and **(±)-72** were diluted to a final concentration of 10 μM using DMEM/F12 media supplemented with 2% FBS, 1x ITS-X, 1x PS, 2.5 nM EGF. The media was aspirated from the 6 well plate containing the cells and the media containing 10 μM of compounds **(±)-69** and **(±)-72** and DMSO vehicle control were added (day 0). After 24 h of culture (day 1), three additional wells were treated with media containing 800 nM Taxol as a positive control. After 48 h of culture (day 2), a concentrated stock of BrdU dissolved in phosphate buffered saline (PBS) was added to each well to achieve a 10 μM final concentration and was incubated for 30 min. For each well, the media was subsequently collected in a 15 mL conical vial and each well was washed with 1 mL of PBS. The PBS was added to the corresponding conical vial containing media and each well was treated with 1 mL of Trypsin-EDTA for 5 min. The single cell suspension was added to the corresponding conical vial containing media. The suspension was spun for 4 min/ 1500 RPM/ 4 °C and the supernatant was removed. The pellet was washed by suspending in 5 mL of chilled HBSS supplemented with 2% BSA and was subsequently spun for 4 min/ 1500 RPM/ 4 °C. The supernatant was removed and the cell pellet was suspended in 300 uL of PBS. With a gentle vortex, 700 uL of

absolute ethanol was added drop wise and was kept at -20 °C overnight. After warming to room temperature, the mixture was spun for 4 min/ 1500 RPM/ 4 °C and the supernatant was removed. The cell pellet was suspended in 1 mL of PBS, spun for 4 min/ 1500 RPM/ 4 °C, and the supernatant was removed. The cell pellet was suspended with 1 mL of 2 N HCl containing 0.5% TritonX-100, incubated at room temperature for 30 min, spun for 4 min/ 1500 RPM/ 4 °C, and the supernatant was removed. The pellet was suspended in 1 mL of 0.1 M of sodium tetraborate decahydrate buffer at pH = 8.0, spun for 4 min/ 1500 RPM/ 4 °C, and the supernatant was removed. The cells were blocked with 1 mL of PBS containing 2% BSA and 0.5% tween-20 for 15 min, spun for 4 min/ 1500 RPM/ 4 °C, and the supernatant was removed. The cells were stained with 300 µL of 10 µg/mL of mouse anti-BrdU primary antibody diluted with PBS containing 2% BSA and 0.5% tween-20 at 4 °C for 1 h. The cells were washed with 1 mL of PBS containing 2 % BSA and 0.5% tween-20, spun for 4 min/ 1500 RPM/ 4 °C, and the supernatant was removed. The cells were stained with 500 µL of Alexa Fluor-488 goat anti-mouse IgG secondary antibody diluted 1:1000 with PBS containing 2% BSA and 0.5% tween-20 at 4 °C for 1 h. The cells were washed with 1 mL of PBS containing 2 % BSA and 0.5% tween-20 for 15 min, spun for 4 min/ 1500 RPM/ 4 °C, and the supernatant was removed. The cells were stained with 250 µL of 5 µg/mL propidium iodide in PBS at room temperature and passed through a 35 µm filter. The suspension was analyzed using a BD FACScan flowcytometer. The percent of cells in G1, S, and G2 were measured and reported as an average ± standard deviation for three independent experiments.

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CHAPTER 4

PALLADIUM-CATALYZED HYDROHETEROARYLATION REACTIONS OF VINYL PHENOLS

Introduction

In recent years, substantial attention has been given to metal-catalyzed hydrofunctionalization reactions with significant focus on hydroheteroarylation reactions.[1-6] When using vinyl arenes as substrates, these reactions rapidly generate molecular complexity around biologically relevant 1,1-diaryl substructures.[7-13] Thus, our group has developed various hydrofunctionalization reactions of styrenes[14-16] and dienes[17] using alkyl and aryl organometallics as reaction partners. We have also reported the hydroalkoxylation of vinyl phenols.[14-19] These reactions have generally been limited to the introduction of simple arenes and alkyl groups as the organometallic reaction partner. Thus, hydrofunctionalization reactions that allow for facile incorporation of broad classes of heteroaromatic compounds are highly desired. Moreover, as discussed in Chapter 3, compounds **69** and **72** demonstrate interesting biological activity against breast cancer cell lines, which provides an additional impetus for the development of a hydrofunctionalization of vinyl phenols with heterocycles to furnish structures analogous to compounds **69** and **72** (Figure 4.1).

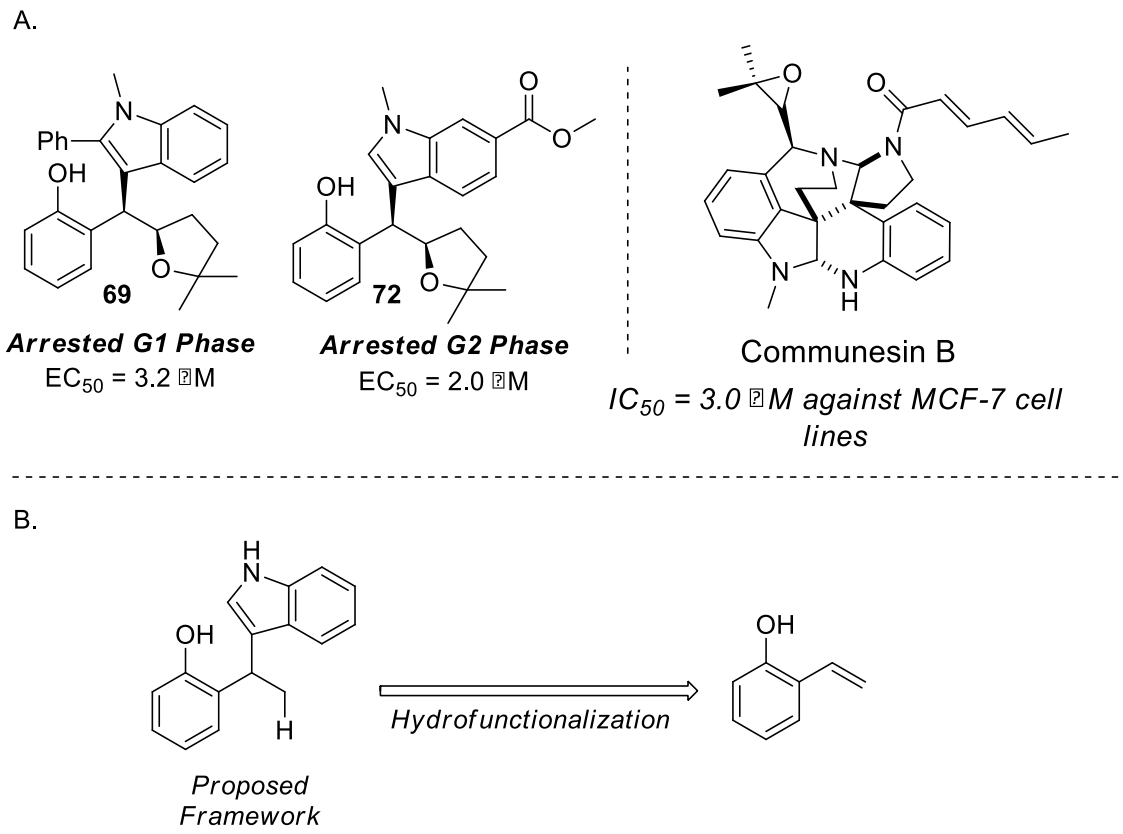


Figure 4.1. Biological activity of compound **69** and **72** against breast cancer cell lines and proposed framework.

Background

Hydrofunctionalization of alkenes with various arenes has been extensively reported in the chemical literature.[20-21] However, reports of hydroheteroarylation of alkenes are scarce.[22-24] In this chapter, relevant recent advances are discussed in detail.

In 2006, Widenhoefer and coworkers reported an interesting hydroheteroarylation reaction of simple alkenes with indoles, using $[PtCl_2(CH_2{=}CH_2)_2]$ as a catalyst.[25] The most striking feature of this method is the use of ethylene in the reaction with indole to give the corresponding Markovnikov addition product in excellent yield (Figure 4.2a). However, when styrenes are used as the substrate, mixtures of Markovnikov and anti-

Markovnikov products were observed (Figure 4.2b). Here, the selectivity is based on the stability of the corresponding benzylic carbocation. Cabocationic intermediate **C** is proposed as the key intermediate, which on reaction with indole leads to product formation (Figure 4.2c).

In 2007, Liu and coworkers reported a Au-catalyzed hydroarylation of styrenes with indoles (Figure 4.3).[26] Interestingly, they observed that catalytic TfOH (which

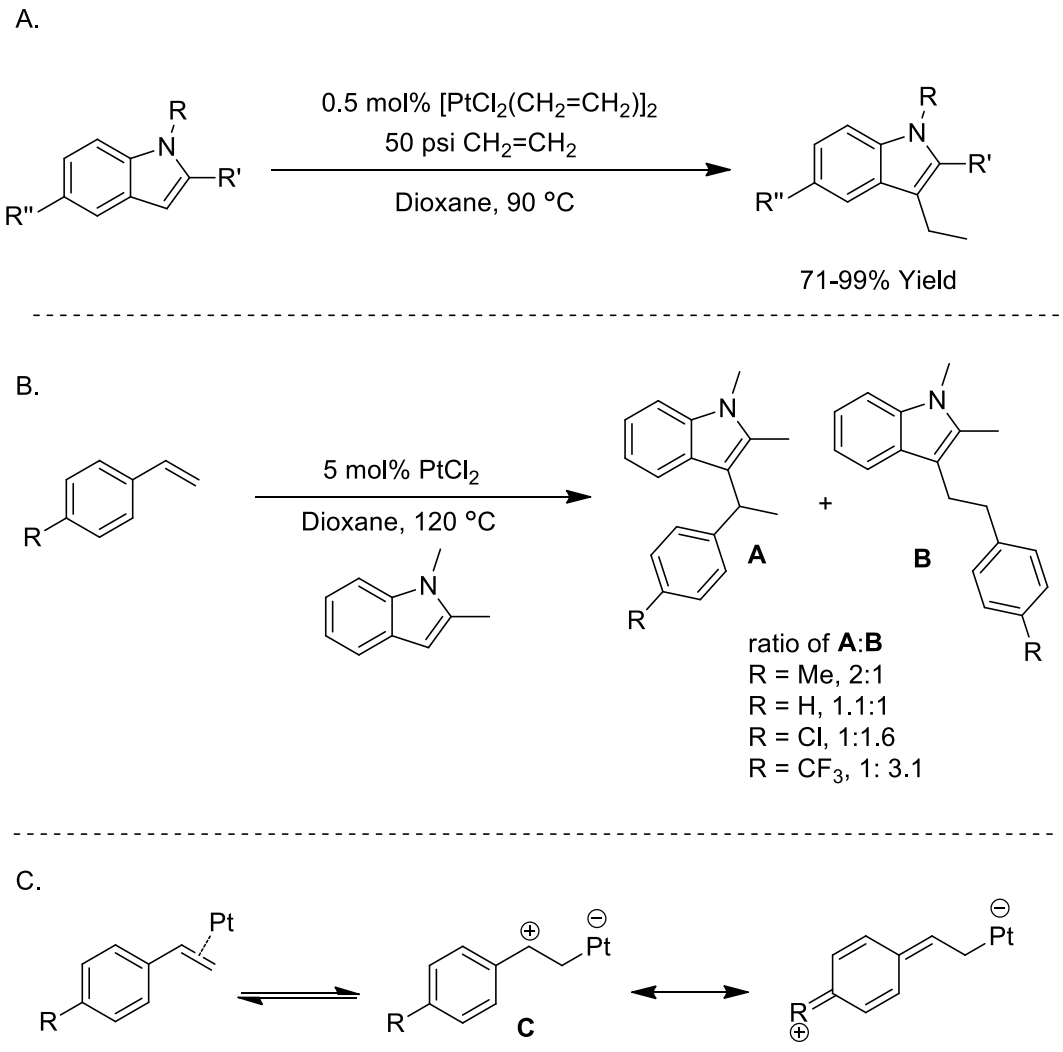
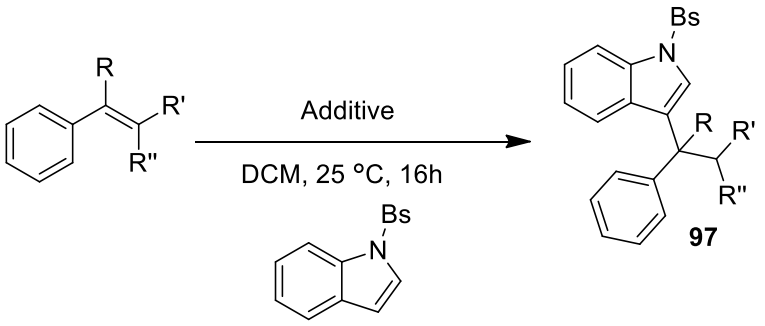


Figure 4.2. Hydroheteroarylation of ethylene and styrenes. Data from Widenhoefer and coworkers.



Additive	Yield of **97**
10 mol % $AuCl_3$/30 mol % AgOTf	93
5-10 mol % $AuBr_3$/30 mol % AgOTf	90
5 mol % TfOH	91

Figure 4.3. Acid catalyzed hydroheteroarylation of alkenes with *N*-phenylsulfonyl-(Bs)-protected indoles. Data from Liu and coworkers.

could form under reported Au-catalyzed conditions after every catalytic cycle) also promoted the reaction. Thus, the scope of this transformation was explored with catalytic amounts of TfOH. The scope of this reaction is limited in both reaction partners. Moreover, only *N*-phenylsulfonyl-(Bs)-protected indoles were used in this report. Later, Che and coworkers reported an improved Au-catalyzed hydroheteroarylation of alkenes with broad substrate scope (Figure 4.4). [27-28] Under optimized conditions, dienes as well as trisubstituted alkenes led to product formation with excellent selectivity. The proposed mechanism for these processes proceeds via the coordination of the alkene carbon-carbon double bond to cationic $[AuPPh_3]^+$, which is attacked by the nucleophilic indole to give a gold complex **B**. This undergoes subsequent protonolysis at the Au-C bond to give the desired coupling product.

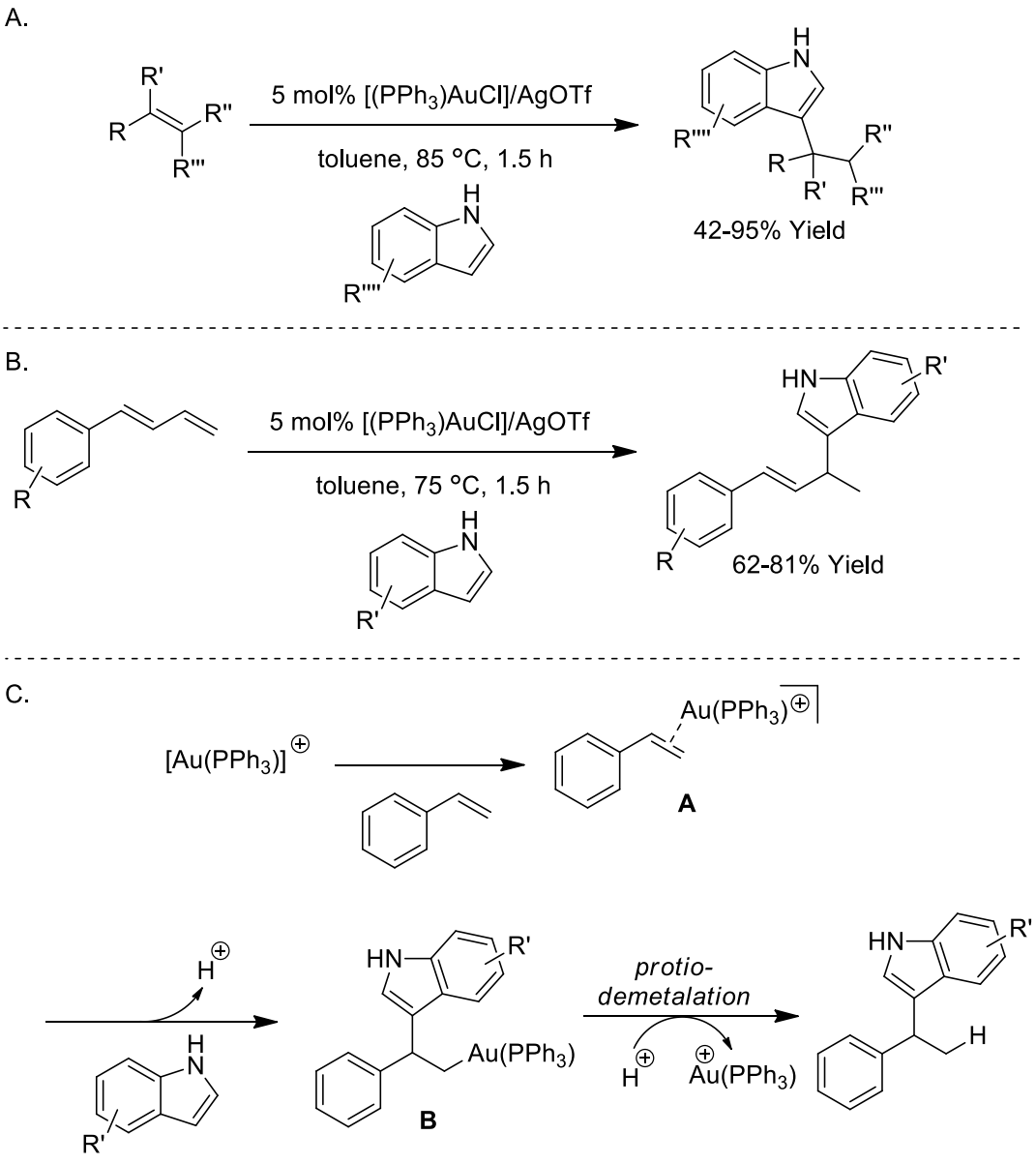


Figure 4.4. Hydroheteroarylation of styrenes, alkenes and dienes. Data from Che and coworkers.

In 2006, Hiyama and coworkers reported an elegant example of a Ni-catalyzed hydroheteroarylation of alkynes (Figure 4.5).[29] The scope of this reaction is broad with respect to heterocycles, however, only symmetrical alkynes gave satisfactory yields of the desired product. More recently, Hiyama and coworkers reported a similar transformation for styrenes with broad scope in both coupling partners (Figure 4.6).[22-24] The proposed mechanism is shown in Figure 4.6. Reversible oxidative addition of an Ar-H bond to the nickel^0/I*i*Mes catalyst results in nickel hydride **A**. The coordination of vinylarene to give intermediate **B** and subsequent hydronickelation leads to 1-arylethylnickel **C**, that reductively eliminates 1,1-diarylethanes irreversibly to regenerate active catalyst.

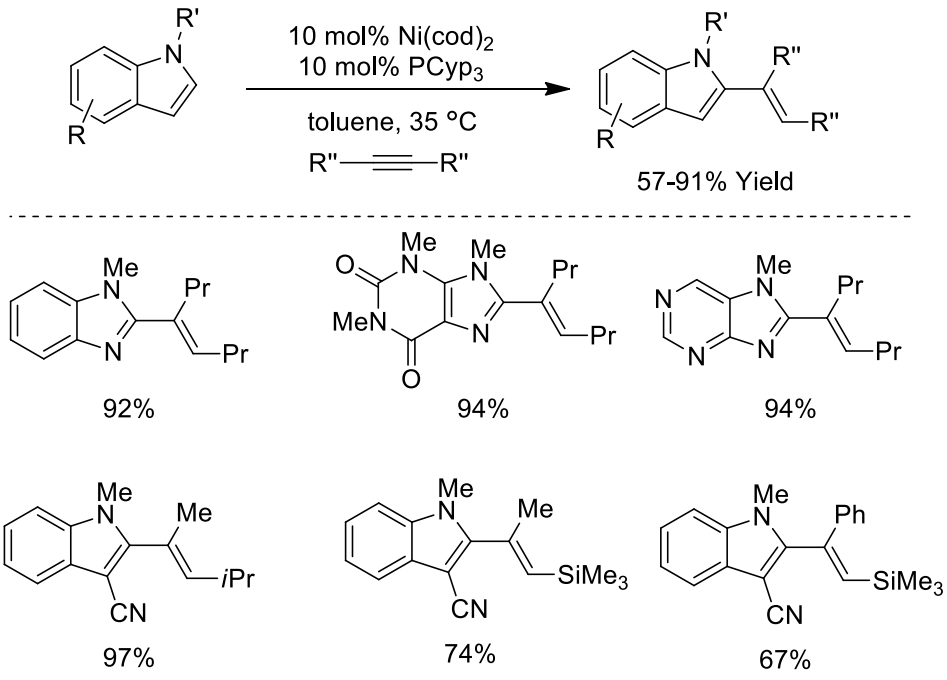


Figure 4.5. Ni-catalyzed hydroheteroarylation of alkynes. Data from Hiyama and coworkers.

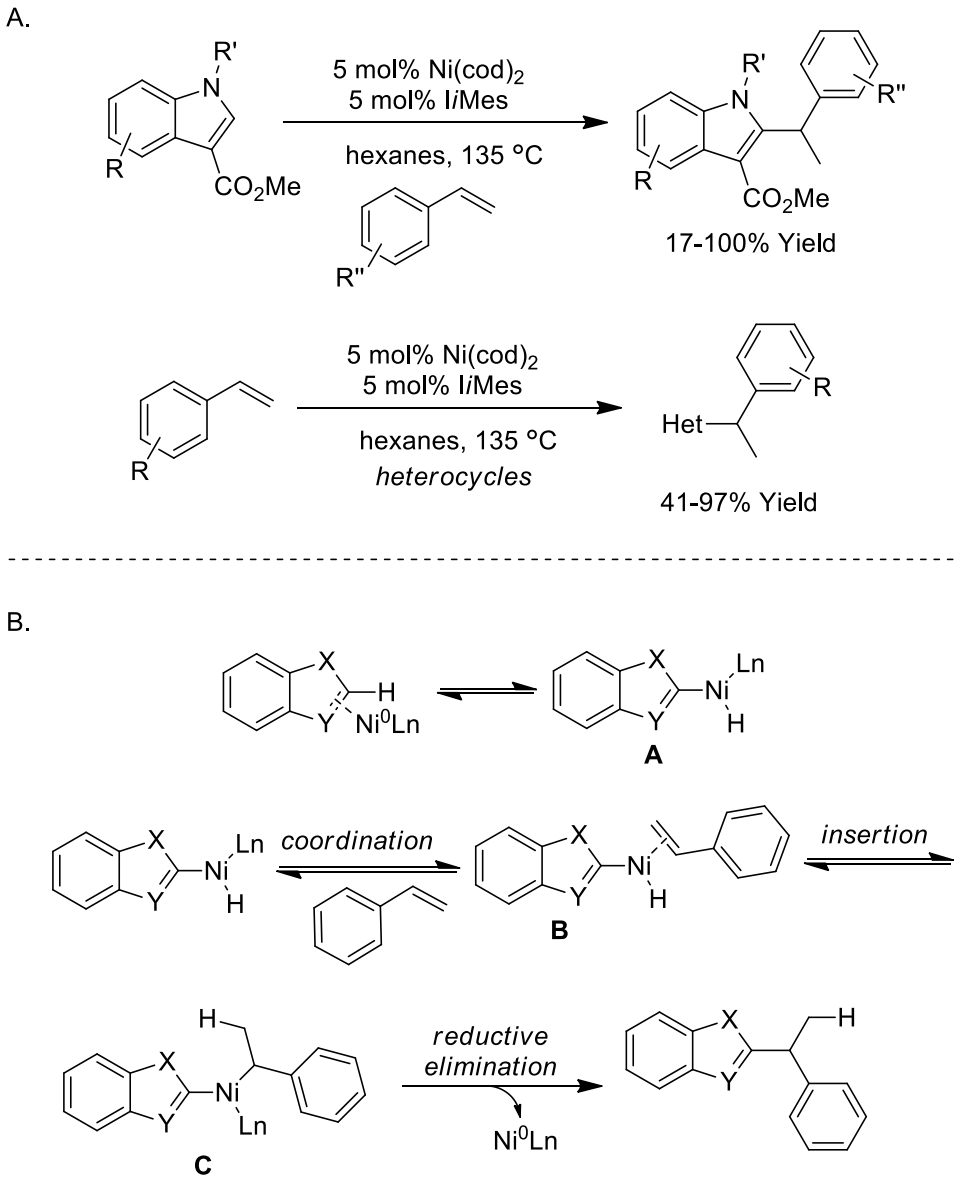


Figure 4.6. Ni-catalyzed hydroheteroarylation reactions of styrenes. Data from Hiyama and coworkers.

Approach

As described above, a number of methods for the hydroheteroarylation of styrenes are available. However, Pd-hydride species have never been utilized for such reactions. Thus, we became interested in developing a Pd-catalyzed hydroheteroarylation of styrenes to yield products analogous to compounds **69** and **72**.

When vinyl phenol **18** was subjected to our previously reported alkene hydroalkoxylation reaction conditions, it gave a poor yield of the desired product using *N*-methyl indole as the nucleophile (Figure 4.7).[18] Furthermore, indole derivatives lacking a protecting group on nitrogen were not tolerated, severely limiting the scope of the process.[30] To overcome these issues, alternative methods to generate Pd-hydrides were explored. We envisioned that oxidative addition of the alkyl halide with Pd^0 would result in the formation of a Pd-alkyl intermediate **A** (Figure 4.8). Because, Pd-alkyl complexes are known to undergo facile β-hydride elimination, intermediate **A** should readily generate Pd-hydride **B** and the corresponding alkene. Insertion of substrate **18** into Pd-hydride **B** would give intermediate **C**, which would decompose to the quinone methide intermediate **D**. The nucleophilic aromatic substitution reaction of indole with intermediate **D** would result in product formation with concomitant release of Pd^0. To our knowledge, this approach to generate Pd-hydrides has never been used to perform hydrofunctionalization reactions of alkenes. Additionally, the proposed Pd^0-catalyzed process should allow for the use of phosphine ligands, which were previously inaccessible because of their facile oxidation to phosphine oxide under oxidative catalysis.

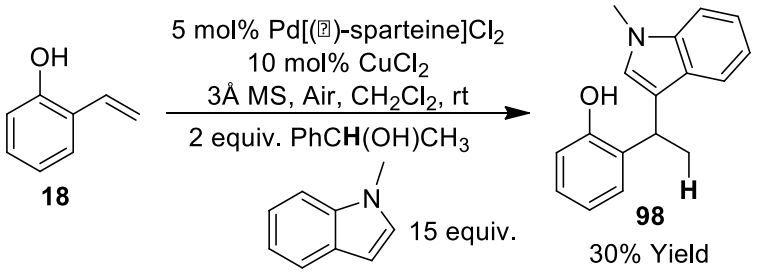


Figure 4.7. Hydroheteroarylation of vinyl phenols under previously reported conditions.

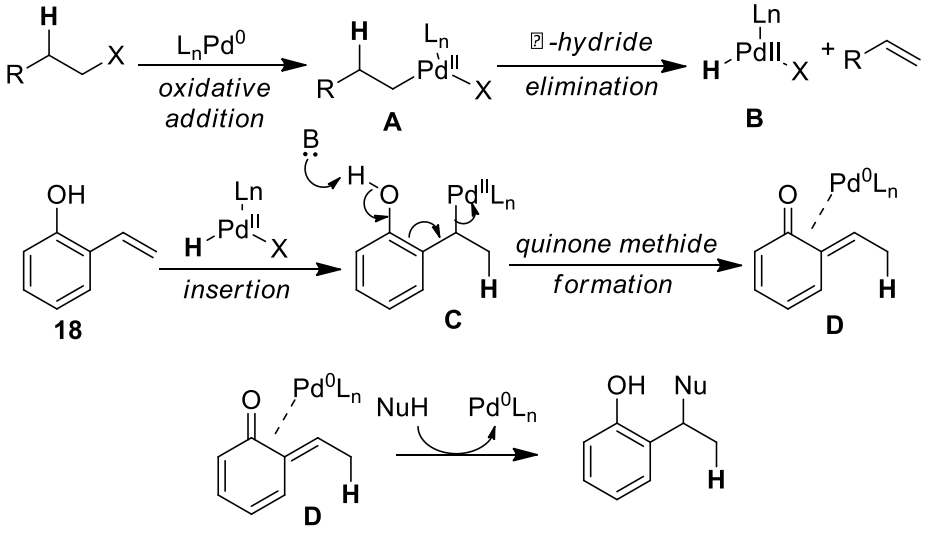
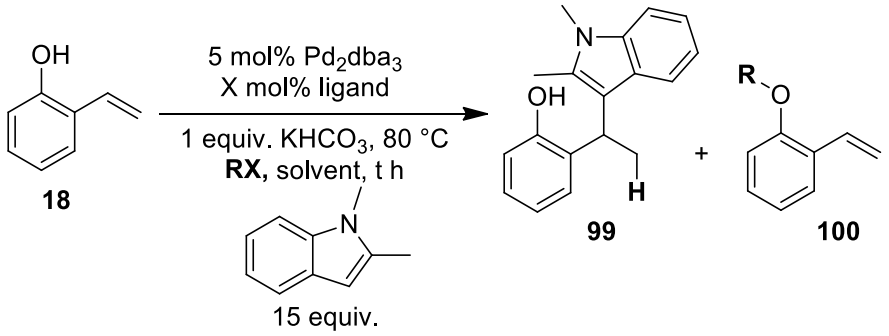


Figure 4.8. Proposed mechanism.

Reaction Optimization and Scope

Initial investigation of this proposed process began with the selection of $Pd_2(dba)_3$ and $P(Cy)_3$, with an alkyl bromide as the potential hydride source based on Fu's reported Pd-catalyzed alkyl-alkyl cross-couplings.[31-32] It should be noted that Fu's conditions are generally designed to slow β-hydride elimination of the Pd-alkyl generated from oxidative addition of an alkyl electrophile. However, when the reaction is performed above 50 °C, β-hydride elimination is observed.[31-32] The reaction of substrate **18** with 1,2-dimethylindole, in the presence of 2 equivalents of $C_{12}H_{25}Br$ as a source of hydride, gave the desired product **99** in 33% yield, with 26% yield of undesired alkylation of phenol **100** (Table 4.1, entry 1). Use of bidentate ligands did not improve the reaction outcome (Table 4.1, entry 2-4). Upon systematic screening, 17 mol% ligand loading was found to give the best result (Table 4.1, compare entries 1 and 5). The formation of **100** is thought to proceed via a nucleophilic substitution of bromide with a phenoxide, and could be potentially overcome by the use of a *sec*-alkyl bromide or an alkyl chloride; in both cases S_N2 processes should be slower. Indeed, cyclohexyl bromide and butyl chloride exclusively gave the desired product but reactions were slower and did not proceed to completion (Table 4.1, entries 6, 7). Due to low cost (~$ 0.03/g) and ease, butyl chloride was chosen as a hydride source. Changing the solvent from toluene to THF or DMA resulted in significantly lower yield of the desired product (Table 4.1, entries 8, 9). Finally, addition of 6 equivalents of butyl chloride and longer reaction time gave 96% conversion with 87% yield of the desired product (Table 4.1, entry 10).

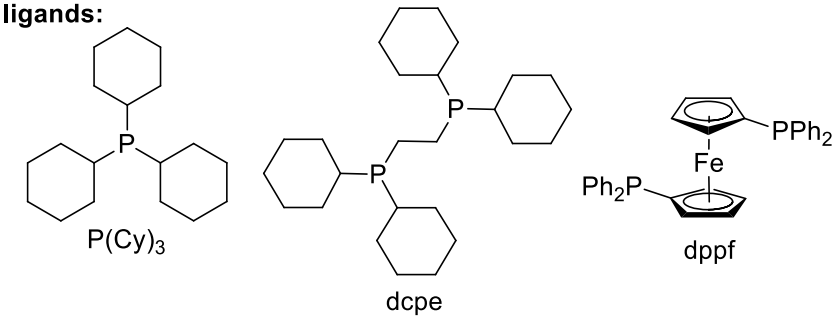
Table 4.1. Optimization of reaction conditions.



Entry	X	Ligand	RX	t (h)	Solvent	% Conv.[a]	% **99**[b]	% **100**[b]
1	20	$P(Cy)_3$	2 equiv. $C_{12}H_{25}Br$	48	Toluene	87	33	26
2	10	dcpe	2 equiv. $C_{12}H_{25}Br$	48	Toluene	71	35	24
3	10	dppf	2 equiv. $C_{12}H_{25}Br$	48	Toluene	68	35	30
4	10	BINAP	2 equiv. $C_{12}H_{25}Br$	48	Toluene	44	20	18
5	17	$P(Cy)_3$	2 equiv. $C_{12}H_{25}Br$	48	Toluene	76	42	26
6	17	$P(Cy)_3$	4 equiv.CyBr	60	Toluene	65	63	<2
7	17	$P(Cy)_3$	4 equiv. C_4H_9Cl	60	Toluene	81	76	<2
8	17	$P(Cy)_3$	4 equiv. C_4H_9Cl	60	THF	85	52	<2
9	17	$P(Cy)_3$	4 equiv. C_4H_9Cl	60	DMA	52	22	<2
10	**17**	**$P(Cy)_3$**	**6 equiv. C_4H_9Cl**	**72**	**Tol**	**96**	**87**	**<2**

[a] The conversion was measured by GC with an internal standard.
[b] The yield was determined by GC. Concentration of the reaction mixture (with respect to **18**): 0.1M.

ligands:

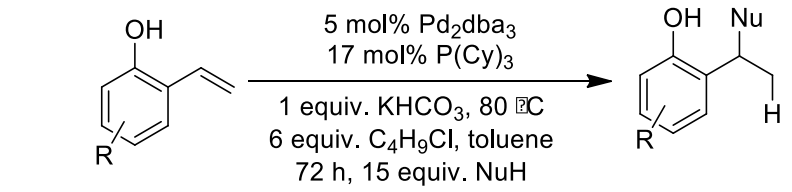


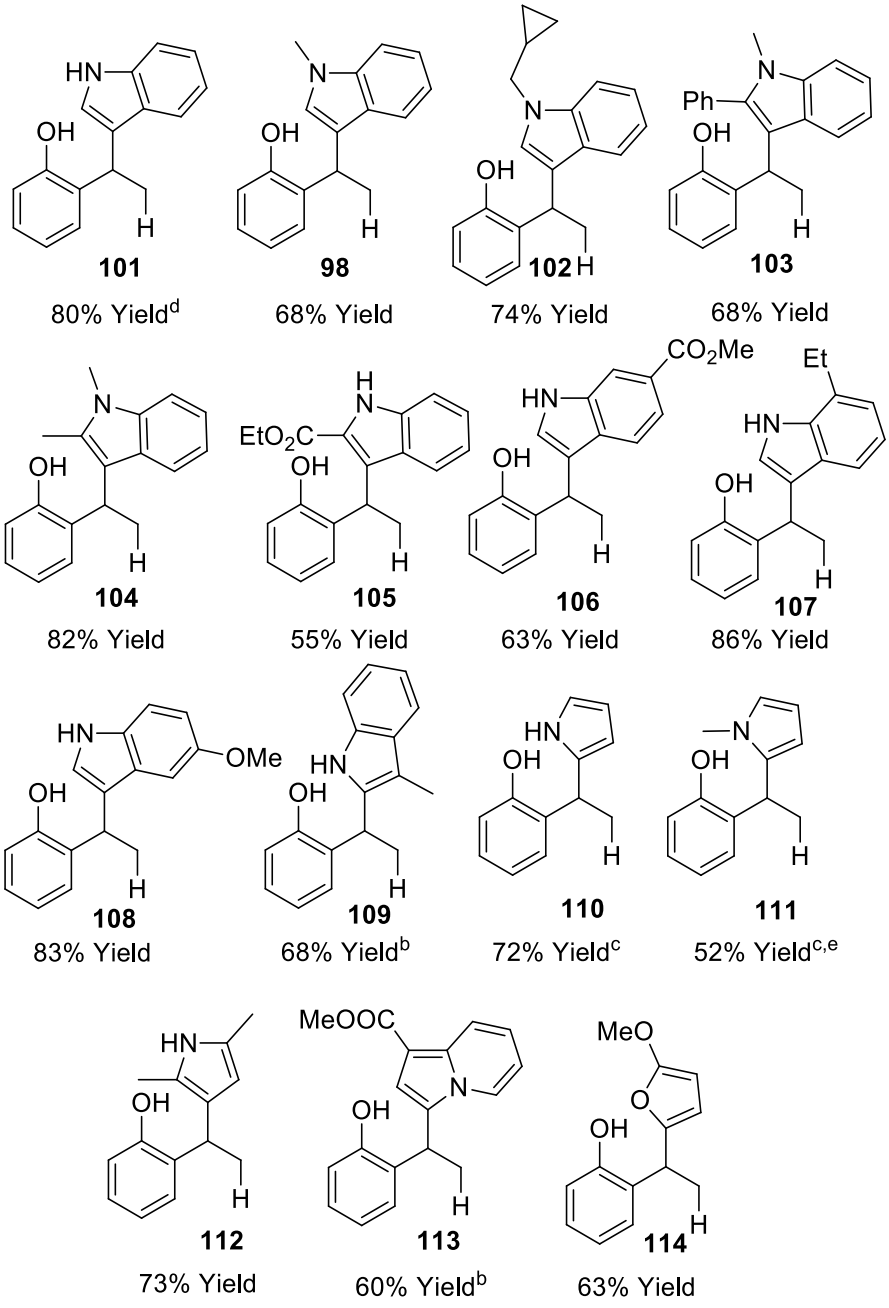
Having optimized the reaction conditions, we moved our attention to evaluate the scope, starting with indole nucleophiles. To our delight, under the optimized conditions unprotected 1*H*-indole gave the product in 80% isolated yield with recovery of the remaining nucleophile in >90% yield (Table 4.2, compound **101**). Unprotected indoles/heteroaromatics as nucleophiles are beneficial because they not only avoid an undesired protection-deprotection sequence, but they also provide flexibility for further synthetic modifications. *N*-alkyl substituted indoles performed well to give products in good yields (Table 4.2, compounds **98**, **102**). Indoles with different steric and electronic parameters, including sterically demanding 2-subtituted indoles are well tolerated under the reaction conditions (Table 4.2, compounds **103**-**108**). Using a 3-substituted indole as the nucleophile, the less nucleophilic 2-position of indole can be functionalized under the optimized reaction conditions (Table 4.2, compound **109**). The nucleophile scope was further expanded to include other nucleophilic heterocycles such as pyrroles, a furan and an indolizine (Table 4.2, compounds **110**-**114**). Indolizines are isoelectronic to indoles and often used in medicinal chemistry to replace indoles during structure-activity relationship (SAR) studies.

Next, the effect of the electronic and steric parameters on the phenol was evaluated. Both electron withdrawing and electron rich vinyl phenols gave good yields of the desired products (Table 4.3, entries **115**-**118**). The *p*-vinylphenol also reacted under the optimized conditions, albeit in low yield (Table 4.3, entry **119**).

To further demonstrate the utility of the developed methodology, an inverse electron demand Diels-Alder reaction with an electron rich cyclic enamine was conducted (See Chapter 1, Figure 4.9). The reaction proceeded smoothly to give

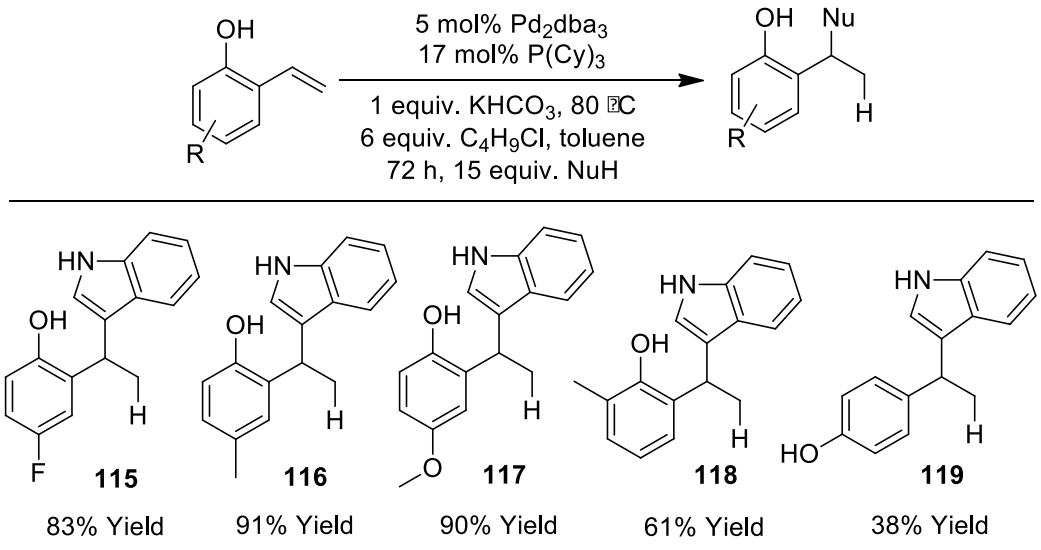
Table 4.2. Scope of exogenous nucleophiles.





a) Yields are averages of at least two runs at 0.3 mmol scale. b) Reactions performed at 100 °C. c) 1 mL of nucleophile was used. d) Performed on a 1.5 mmol scale. e) Ratio of C2/C3 alkylation = 4:1

Table 4.3. Scope of vinyl phenols.



a) Yields are averages of at least two runs at 0.3 mmol scale.

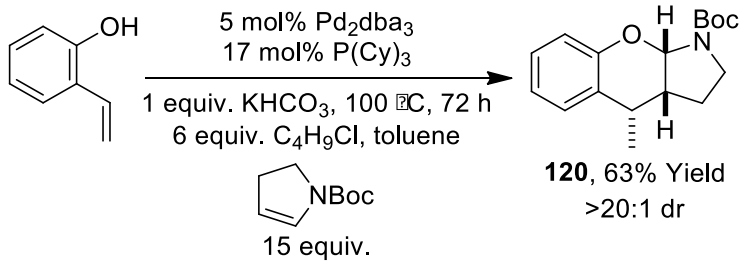


Figure 4.9. Inverse electron demand Diels-Alder reaction.

chromane derivative **120** in 63% yield as a single diastereomer. This transformation showcases the effectiveness of the method to generate relatively complex frameworks from a simple substrate, in a single step, with excellent diastereoselectivity. Nucleophiles that failed to provide the desired hydrofunctionalized products are shown in Figure 4.10.

Accessing Interesting Indole Core Structures

The phenol, which is a mechanistic requirement for quinone methide formation, provides a handle for further derivatization of products to biologically relevant scaffolds as demonstrated in Figure 4.11. Conversion of phenol **101** to the corresponding triflate, followed by an intramolecular Heck reaction gives the potent antioxidant **121** in 87% yield (Figure 4.11a).[33-34] The tetracyclic indanoindole scaffolds are also found in various biologically active compounds and exhibits a range of biological activity.[33,35-47] Furthermore, the indole core (in **121**) is still intact and allows for further derivatization. Compound **101** can also be converted to compound **122** in excellent yield (Figure 4.11b), which is structurally equivalent to a hydroheteroarylated styrene and is a common scaffold found in many pharmacophores.[7-13] Furthermore, the treatment of compound **101** with NBS gives tetracyclic compound **123** in excellent yield (Figure 4.11c).

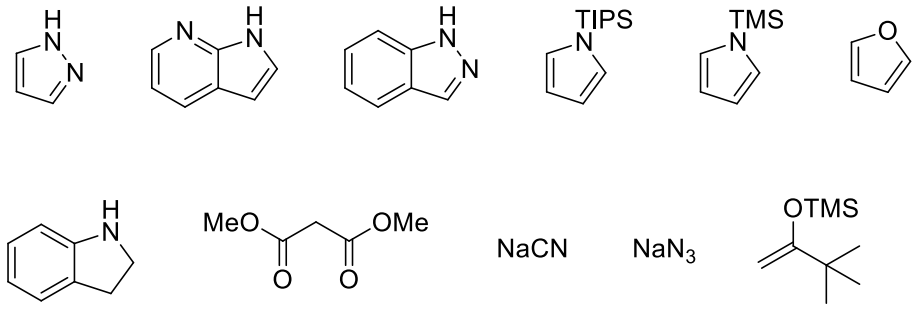
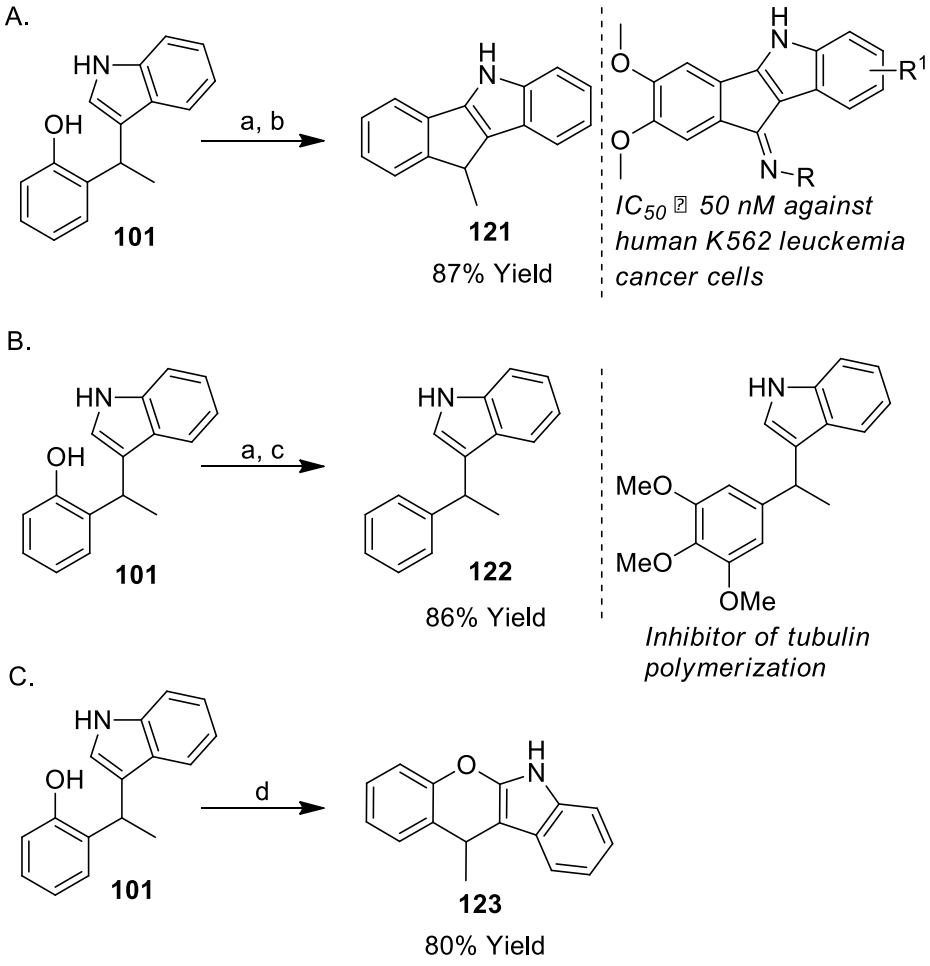


Figure 4.10. Failed nucleophiles.



a) 2,6-lutidine, Tf_2O, DCM, -78 °C to rt, 90%; b) 10 mol% Pd_2dba_3, 20 mol% dppb, 10 equiv. KOAc, DMA, 100 °C; c) $Pd(OH)_2/C$, H_2, Et_3N, MeOH:EtOAc (3:1); d) NBS, PPTS, DCM, -78 °C to rt.

Figure 4.11. Product derivatization to provide biologically relevant framework.

Mechanistic Considerations

To support our mechanistic hypothesis, a control experiment in the absence of the alkyl chloride was performed (Figure 4.12a). To our surprise, product formation was still observed presumably via a 1,5-sigmatropic rearrangement, albeit in lower yields.[48] Additionally, a reaction of the vinyl phenol with indoles in the absence of any catalyst was performed to achieve a similar yield (Figure 4.12b). It should be noted that such 1,5-

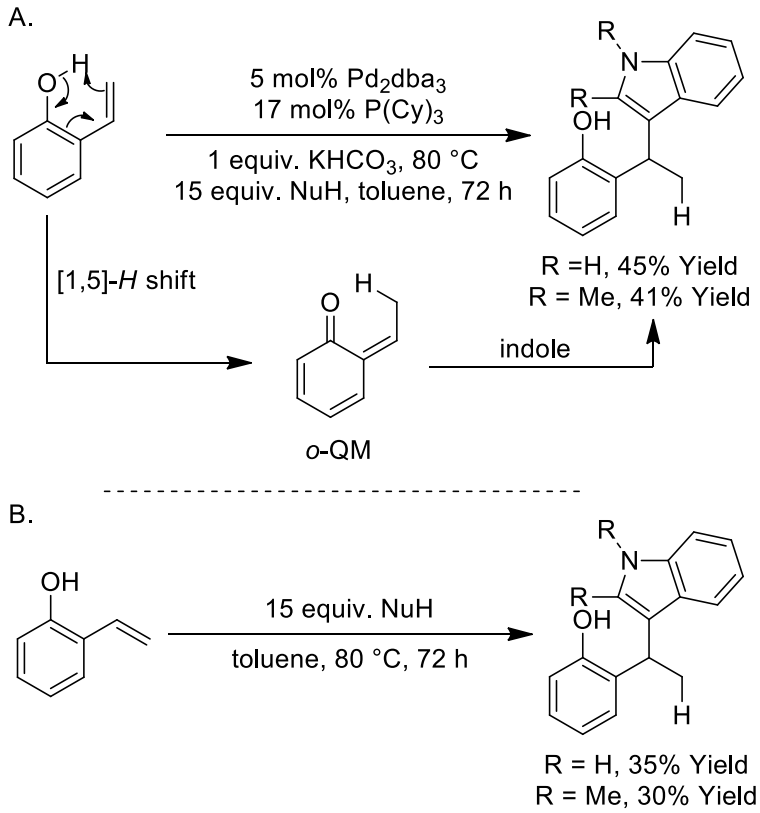


Figure 4.12. Control experiments.

sigmatropic rearrangements are not commonly used for *o*-QM formation and functionalization and often require more forcing conditions. Additionally, the observed 1,5-sigmatropic rearrangement is promising and could provide an alternative method to utilize reaction partners, that are currently not compatible with known methods for *o*-QM formation and functionalization.

To probe the origin of the hydrogen incorporated into the desired product **125,** deuterium labeling experiments were performed. The use of deuterated phenol **124** under standard reaction conditions resulted in <5% deuterium incorporation in the desired product (Figure 4.13a). However, reaction of deuterated phenol in the presence of a deuterated alkyl halide gave >95% D-incorporation in the desired product (Figure 4.13b).

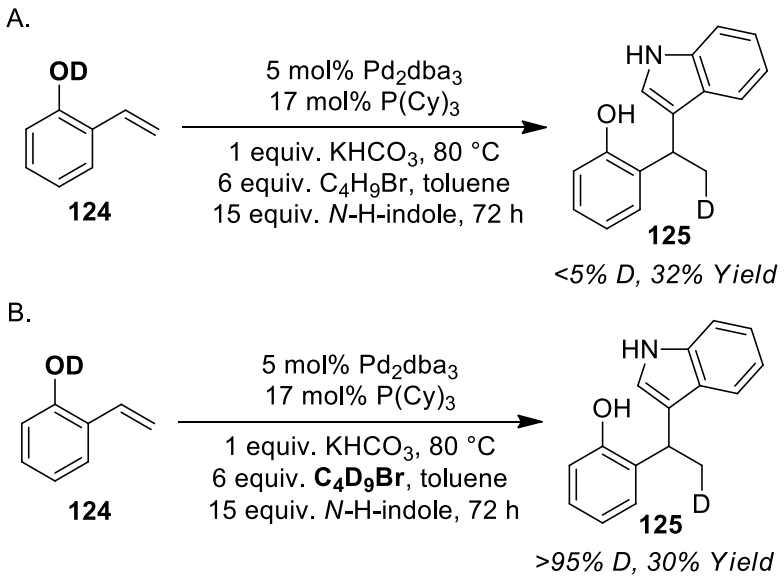


Figure 4.13. Deuterium labeling experiments.

These experiments suggest that in the presence of the alkyl halide a mechanism involving a Pd-hydride dictates the product formation over a 1,5-sigmatropic rearrangement. The deuterium labelling experiments in conjunction with the above control experiments (Figure 4.12) suggest that both of the proposed reaction pathways could be contributing to product formation.[49]

Conclusion

We have successfully utilized a Pd-hydride, generated from an alkyl halide, in the hydrofunctionalization reaction of vinyl phenols. This method allows for the use of various heterocycles as exogenous nucleophiles. Moreover, the products obtained can be rapidly processed to biologically relevant scaffolds. In addition, they are analogous to compounds **69** and **72** and are currently being screened against various cancer cell lines. The method serves as a proof-of-concept, and currently, we are applying this approach to various alkene hydrofunctionalization reactions.

Experimental

General Information

Unless otherwise noted, all reactions were run under a nitrogen atmosphere with stirring. Toluene, dichloromethane, and THF were dried before use by passing through a column of activated alumina. All other reagents (including indoles) were purchased from commercial sources and used without further purification. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained either with potassium permanganate, *p*-anisaldehyde, phosphomolybdic acid or vanillin. Flash column chromatography was performed with EcoChrom MP Silitech 32-63D 60Å silica gel, slurry packed with solvents indicated in glass columns. Nuclear magnetic resonance spectra were acquired at 400 MHz for ^{1}H, and 100 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million downfield relative to the line of $CHCl_3$ singlet at 7.26 ppm. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center-line of the $CDCl_3$ triplet at 77.2 ppm. The abbreviations s, d, t, q, td, dd and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, triplet of doublet, doublet of doublet and multiplet, respectively. IR spectra were recorded using a Nicolate FT-IR instrument. Glassware for all reactions was oven-dried at 110 ^{o}C and cooled while purging with nitrogen prior to use.

Substrate Synthesis

Representative Procedure

To an oven-dried 500 mL round bottom flask equipped with a stir bar were added 34.2 g of phosphine salt (96.0 mmol, 2.30 equiv.) and 300 mL toluene. To this was added a solution of 10.80 g KO^{t}Bu (96.9 mmol, 2.33 equiv.) in 80 mL of THF dropwise via cannulation. The reaction mixture slowly turned a deep red color over 4 h. The mixture was cooled to –0 °C and 5.00 g of salicylaldehyde (41.1 mmol, 1.00 equiv.), dissolved in 20 mL of toluene, was added dropwise. The mixture was allowed to slowly warm to ambient temperature and stirred 8 hours then quenched with 50 mL of saturated NH_4Cl solution. The mixture was diluted with 100 mL of diethyl ether and washed with 100 mL (2 x 50 mL) of water and 60 mL of brine. The organic layer was dried over $MgSO_4$, filtered, and the solvent removed in vacuo. The crude mixture was purified by flash silica-gel column chromatography with 10%-20% EtOAc/Hexanes as eluent.

^{1}H-NMR was matched with literature ^{1}H-NMR for all substrates.[18]

Reaction Optimization (see Table 4.1 in text)

Entry 1, Table 4.1

In the glovebox, to a 2.5 dram vial equipped with a stir bar were added 4.7 mg Pd_2dba_3 (0.0050 mmol, 0.050 equiv.), 5.6 mg $P(Cy)_3$ (0.020 mmol, 0.20 equiv.) and 200 µL of toluene. The reaction mixture was allowed to stir for ca.15 min. In a separate 2.5 dram vial equipped with a stir bar was added 50.0 mg of alkyl bromide (0.02 mmol, 2.0 equiv.), 10.0 mg of $KHCO_3$ (0.10 mmol, 1.0 equiv.), 217.5 mg of 1,2-dimethylindole (1.500 mmol, 15.00 equiv.) and 200 µL of standard solution of **3** (0.10 mmol, 1.00 equiv.) in toluene (*standard solution*: 18.0 mg of **3**, and 10 µL of undecane as internal

standard in 300 μL of toluene). To this an additional 600 μL of toluene and the catalyst solution were added. The vial was capped and was heated to 80 °C for 48 h in an oil bath. At this point the vial was open to air, and the reaction was analyzed by GC using an internal standard to calculate conversion as well as yield of various products.

Entry 2, Table 4.1

The same procedure as described for entry **1** was used, except 4.22 mg dcpe (0.0100 mmol, 0.100 equiv.) was added as ligand.

Entry 3, Table 4.1

The same procedure as described for entry **1** was used, except 5.84 mg dppf (0.0100 mmol, 0.100 equiv.) was added as ligand.

Entry 4, Table 4.1

The same procedure as described for entry **1** was used, except 6.20 mg BINAP (0.0100 mmol, 0.100 equiv.) was added as ligand.

Entry 5, Table 4.1

In the glovebox, to a 2.5 dram vial equipped with a stir bar were added 4.7 mg Pd_2dba_3 (0.0050 mmol, 0.050 equiv.), 5.0 mg $P(Cy)_3$ (0.017 mmol, 0.17 equiv.) and 200 μL of toluene. The reaction mixture was allowed to stir for *ca.*15 min. In a separate 2.5 dram vial equipped with a stir bar was added 50.0 mg of alkyl bromide (0.02 mmol, 2.0 equiv.), 10.0 mg of $KHCO_3$ (0.10 mmol, 1.0 equiv.) and 217.5 mg of 1, 2-dimethylindole (1.500 mmol, 15.00 equiv.) and 200 μL of standard solution of **3** (0.10 mmol, 1.00 equiv.) in toluene (*standard solution*: 18.0 mg of **3**, and 10 μL of undecane as internal standard in 300 μL of toluene). To this, an additional 600 μL of toluene and the catalyst

solution were added. The vial was capped and was heated to 80 °C for 48 h in an oil bath. At this point the vial was open to air and the reaction was analyzed by GC using an internal standard to calculate conversion as well as yield of various products.

Entry 6, Table 4.1

The same procedure as described for entry **5** was used, except 49.0 μL CyBr (0.40 mmol, 4.00 equiv.) was added and the reaction was run for 60 h.

Entry 7, Table 4.1

The same procedure as described for entry **5** was used, except 19.0 μL C_4H_9Cl (0.40 mmol, 4.00 equiv.) was added and the reaction was run for 60 h.

Entry 8, Table 4.1

The same procedure as described for entry **5** was used, except THF was used as solvent.

Entry 9, Table 4.1

The same procedure as described for entry **5** was used, except DMA was used as solvent.

Entry 10, Table 4.1

The same procedure as described for entry **5** was used, except 28.0 μL C_4H_9Cl (0.60 mmol, 6.00 equiv.) was added and the reaction was run for 72 h.

Substrate Scope

General Procedure

In the glovebox, to a 2.5 dram vial equipped with a stir bar was added 14.1 mg Pd_2dba_3 (0.015 mmol, 0.050 equiv.), 15.0 mg $P(Cy)_3$ (0.051 mmol, 0.17 equiv.) and 1.0 mL of toluene. The reaction mixture was allowed to stir for ca.15 min. In a separate 25 mL sealed flask equipped with a stir bar was added 165.0 μL of C_4H_9Cl (1.80 mmol, 6.0 equiv.), 30.0 mg of $KHCO_3$ (0.30 mmol, 1.0 equiv.) and 526.5 mg of 1*H*-indole (4.500 mmol, 15.00 equiv.) and 36.0 mg of **18** (0.30 mmol, 1.00 equiv.) in 2.0 mL of toluene. To this, catalyst solution was added. The flask was capped and was heated to 80 °C for 72 h, in oil bath, and diluted with 10 mL of EtOAc. The reaction mixture was then passed through silica gel to remove metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Note: Most of the compounds were found to be light sensitive and turned brown, yellow or green over a period of time.

Preparation of 101

The same procedure as that of general procedure was followed. *This reaction was scaled up to 1.5 mmol.* Yield = 80% (average of two run), R_f= 0.30 w/ 20% EtOAC/Hex, pale green solid, M.P. = 95-97 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.96 (s,1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.32 (dt, *J* = 7.6 Hz, *J* = 1.8 Hz, 2 H), 7.21-7.13 (m, 2 H), 7.06-7.02 (m, 1 H), 6.96 (ddd, *J* = 14.4 Hz, *J* = 6.9 Hz, *J* = 1.5 Hz, 2 H), 6.78 (dd, *J* = 8.0 Hz, *J* = 1.1 Hz, 1 H), 5.28 (s, 1 H), 4.54 (q, *J* = 7.1 Hz, 1 H), 1.75 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.3, 137.1, 131.7, 128.6, 127.8, 126.8, 122.7, 121.5,

121.1, 119.9, 119.8, 119.6, 116.6, 111.5, 32.4, 20.5. IR 3406, 2963, 1584, 1451, 1335, 1095, 738 cm^{-1}. HRMS $C_{16}H_{16}NO$ $(M)^+$ calcd. 238.1232, obsvd. 238.1239.

Preparation of 98

The same procedure as that of general procedure was followed except 589 mg of *N*-methylindole **(**4.50mmol, 15.0 equiv.) was added. Yield = 68% (average of two run), R_f = 0.35 w/ 20% EtOAC/Hex, sticky oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.40 (dt, *J* = 8.0 Hz, *J* = 1.0 Hz, 1 H), 7.34-7.29 (m, 1 H), 7.23 (ddd, *J* = 8.1 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz, 1 H), 7.15 (td, *J* = 7.7 Hz, *J* = 1.6 Hz, 1 H), 7.03 (ddd, *J* = 8.0 Hz, *J* = 6.9 Hz, 1.0 Hz, 1 H), 6.95 (dt, *J* = 7.4 Hz, *J* = 1.3 Hz, 1 H), 6.91 (d, *J* = 1.0 Hz, 1 H), 6.78 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 5. 26 (s, 1 H), 4.53 (q, *J* = 7.1 Hz, 1 H), 3.74 (s, 3 H), 1.75 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.3, 137.9, 131.7, 128.5, 127.8, 127.2, 126.2, 122.3, 121.0, 119.9, 119.3, 117.9, 116.6, 109.6, 33.0, 32.4, 20.6. IR 3356, 2963, 1737, 1612, 752 cm^{-1}. HRMS $C_{17}H_{17}NO$ $(M+Na)^+$ calcd. 274.1208, obsvd. 274.1205.

Preparation of 102

The same procedure as that of general procedure was followed except 770.0 mg of indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 74% (average of two run), R_f = 0.35 w/ 20% EtOAC/Hex, colorless liquid, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.36 (m, 3 H), 7.23-7.19 (m, 1 H), 7.17-7.12 (m, 1 H), 7.10 (s, 1 H), 7.02 (ddt, *J* = 7.9 Hz, *J* = 7.0 Hz, 0.9 Hz, 1 H), 6.95 (dt, *J* = 7.5 Hz, *J* = 0.9 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 5. 34 (s, 1 H), 4.53 (q, *J* = 7.1 Hz, 1 H), 3.95 (d, *J* = 6.8 Hz, 2 H), 1.77 (d, *J* = 7.1 Hz, 3 H), 1.32-1.22 (m, 1 H), 0.65-0.60 (m, 2 H), 0.38-0.34 (m, 2 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.5, 137.5, 131.8, 128.6, 127.8, 127.3, 124.9, 122.3, 121.0, 120.1, 119.3,

117.9, 116.6, 109.8, 50.9, 32.7, 20.6, 11.5, 4.4, 4.3. IR 3419, 2963, 2928, 1611, 1451, 1219, 733 cm^{-1}. HRMS $C_{20}H_{22}NO$ $(M)^+$ calcd. 292.1701, obsvd. 292.1704.

Preparation of 103

The same procedure as that of general procedure was followed except 932.8 mg of *N*-methyl-2-phenyl-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 68% (average of two run), R_f= 0.47 w/ 20% EtOAC/Hex, colorless solid. M.P. = 169-171 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.45 (m, 4 H), 7.34-7.29 (m, 2 H), 7.23 -7.19 (m, 1 H), 7.12-7.09 (m, 1 H), 7.02-6.91 (m, 3 H), 6.69 (dd, *J* = 7.9 Hz, *J* = 1.2 Hz, 1 H), 5. 17 (s, 1 H), 4.31 (q, *J* = 7.1 Hz, 1 H), 3.56 (s, 3 H), 1.75 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.8, 137.9, 137.8, 131.4, 130.8, 129.0, 128.9, 127.7, 127.0, 126.0, 122.3, 120.6, 119.7, 116.2, 114.7, 109.8, 31.0, 30.9, 20.7. IR 3311, 2929, 2851, 1590, 1448, 1328, 1232, 1071, 1023, 749 cm^{-1}. HRMS $C_{23}H_{22}NO$ $(M)^+$ calcd. 328.1701, obsvd. 328.1704.

Preparation of 104

V except 653.4 mg of 1,2-dimethyl-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 82% (average of two run), R_f= 0.45 w/ 20% EtOAC/Hex, colorless solid, M.P. = 94-96 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.53 (dt, *J* = 7.6 Hz, *J* = 1.1 Hz, 1 H), 7.31 (d, *J* = 7.9 Hz, 1 H), 7.25 (d, *J* = 8.2 Hz, 1 H), 7.19-7.12 (m, 2 H), 7.04-6.95 (m, 2 H), 6.76 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1 H), 5. 25 (s, 1 H), 4.48 (q, *J* = 7.2 Hz, 1 H), 3.63 (s, 3 H), 2.32 (s, 3 H), 1.73 (d, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.0, 133.7, 131.2, 127.8, 126.9, 126.2, 121.3, 120.7, 119.4, 118.8, 116.4, 112.0, 109.1, 30.9, 29.7, 20.1, 10.5. IR 3406, 2970, 1609, 1470, 1452, 739 cm^{-1}. HRMS $C_{18}H_{20}NO$ $(M)^+$ calcd. 266.1545, obsvd. 266.1546.

Preparation of 105

V except 851.4 mg of ethyl 1*H*-indole-2-carboxylate **(**4.500 mmol, 15.0 equiv.) was added. Yield = 53% (average of two run), R_f = 0.21 w/ 33% EtOAC/Hex, colorless solid, M.P. = 135-137 °C ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.68 (s, 1 H), 7.77 (d, *J* = 8.3 Hz, 1 H), 7.69 (d, *J* = 6.9 Hz, 1 H), 7.32 (dd, *J* = 8.3 Hz, *J* = 0.8 Hz, 1 H), 7.25 (d, *J* = 8.6 Hz, 1 H), 7.11-7.07 (m, 1 H), 7.03-6.94 (m, 2 H), 6.82 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1 H), 5.32 (q, *J* = 7.1 Hz, 1 H), 4.40-4.32 (m, 1 H), 4.26-4.18 (m, 1 H), 1.85 (d, *J* = 7.1 Hz, 3 H), 1.31 (td, *J* = 7.1 Hz, *J* = 0.8 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 164.3, 155.4, 137.0, 129.8, 128.3, 127.4, 126.6, 126.4, 123.2, 122.0, 120.8, 120.6, 117.0, 112.7, 62.3, 30.2, 20.4, 14.8. IR 3327, 2924, 1716, 1245, 748 cm^{-1}. HRMS $C_{19}H_{19}NO_3$ $(M+Na)^+$ calcd. 332.1263, obsvd. 332.1263.

Preparation of 106

The same procedure as that of general procedure was followed except 788.4 mg of methyl 1*H*-indole-6-carboxylate **(**4.500 mmol, 15.0 equiv.) was added. Yield = 63% (average of two run), R_f = 0.31 w/ 50% EtOAC/Hex, colorless solid, M.P. = 88-90 °C. ^{1}H-NMR (400 MHz, Acetone-D_6) δ = 8.33 (s, 1 H), 8.12 (s, 1 H), 7.60 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1 H), 7.49 (dd, *J* = 2.7 Hz, *J* = 0.9 Hz, 1 H), 7.43 (d, *J* = 8.4 Hz, 1 H), 7.00-6.96 (m, 2 H), 6.89 (dd, *J* = 7.4 Hz, *J* = 0.9 Hz, 1 H), 6.68 (td, *J* = 7.4 Hz, *J* = 1.1 Hz, 1 H), 4.88 (q, *J* = 7.1 Hz, 1 H), 3.84 (s, 3 H), 1.66 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, Acetone-D_6) δ = 167.6, 154.4, 136.5, 133.3, 130.8, 128.1, 126.8, 125.7, 123.2, 121.1, 119.8, 119.4, 119.0, 115.3, 113.6, 51.2, 20.6. IR 3405, 2962, 1715, 1472, 1304, 1219, 753 cm^{-1}. HRMS $C_{18}H_{18}NO_3$ $(M)^+$calcd. 296.1287, obsvd. 296.1291.

Preparation of 107

The same procedure as that of general procedure was followed except 653.4 mg of 7-ethyl-1*H*-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 86% (average of two run), R_f = 0.42 w/ 20% EtOAC/Hex, colorless solid, M.P. = 98-100 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.98 (s, 1 H), 7.31 (dd, *J* = 8.3 Hz, *J* = 1.7 Hz, 1 H), 7.27 (dd, *J* = 7.6 Hz, *J* = 0.7 Hz, 1 H), 7.13 (td, *J* = 7.7 Hz, *J* = 1.7 Hz, 1 H), 7.04-6.97 (m, 3 H), 6.94 (td, *J* = 7.5 Hz, *J* = 1.3 Hz, 1 H), 6.77 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 5.26 (bs, 1 H), 4.52 (q, *J* = 7.1 Hz, 1 H), 2.82 (q, *J* = 7.6 Hz, 2 H), 1.74 (d, *J* = 7.1 Hz, 3 H), 1.34 (t, *J* = 7.6 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.3, 136.0, 131.7, 128.5, 127.8, 126.8, 126.6, 121.3, 121.1, 121.0, 120.2, 120.1, 117.6, 116.6, 32.6, 24.1, 20.5, 14.0. IR 3415, 2963, 2930, 1587, 1450, 1217, 784 cm^{-1}. HRMS $C_{18}H_{20}NO$ $(M)^+$calcd. 266.1545, obsvd. 266.1545.

Preparation of 108

The same procedure as that of general procedure was followed except 780.0 mg of 5-methoxy-1*H*-indole **(**4.500 mmol, 15.0 equiv.) was added. Yield = 83% (average of two run), R_f = 0.22 w/ 20% EtOAC/Hex, colorless solid, M.P. = 148-150 C ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.97 (s, 1 H), 7.33 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1 H), 7.21 (d, J = 8.7 Hz, 1 H), 7.14 (td, *J* = 7.6 Hz, *J* = 1.6 Hz, 1 H), 7.02 (d, *J* = 1.6 Hz, 1 H), 6.95 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 6.86 (dd, *J* = 8.7 Hz, *J* = 2.4 Hz, 1 H), 6.82-6.77 (m, 2 H), 5.32 (bs, 1 H), 4.50 (q, *J* = 7.1 Hz, 1 H), 3.72 (s, 3 H), 1.75 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.3, 154.0, 132.3, 131.6, 128.6, 127.8, 127.2, 122.3, 121.1, 119.2, 116.6, 112.8, 112.2, 101.8, 55.9, 32.5, 20.4. IR 3410, 2963, 1583, 1451, 1272, 1208, 743 cm^{-1}. HRMS $C_{17}H_{18}NO_2$ $(M)^+$ calcd. 268.1338, obsvd. 268.1342.

Preparation of 109

The same procedure as that of general procedure was followed except 590.4 mg of 3-methyl-1*H*-indole **(**4.500 mmol, 15.0 equiv.) was added and reaction was heated to 100 °C. Yield = 68% (average of two run), R_f = 0.45 w/ 20% EtOAC/Hex, colorless thick liquid, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.52-7.50 (m, 1 H), 7.23-7.21 (m, 1 H), 7.08-7.03 (m, 2 H), 6.98-6.94 (m, 2 H), 6.79 (t, *J* = 7.5 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 5.84 (q, *J* = 7.0 Hz, 1 H), 4.95 (bs, 1 H), 2.28 (s, 3 H), 1.78 (d, *J* = 7.0 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 153.2, 136.6, 129.4, 129.0, 128.8, 128.7, 126.9, 122.7, 121.8, 121.4, 119.2, 116.1, 111.2, 110.1, 49.7, 20.2, 10.0. IR 3507, 2975, 2931, 1609, 1456, 737 cm^{-1}. HRMS $C_{17}H_{18}NO$ $(M)^+$ calcd. 252.1388, obsvd. 252.1391.

Preparation of 110

The same procedure as that of general procedure was followed except 1 mL of 1*H*-pyrrole was added. Yield = 72% (average of two run), R_f = 0.35 w/ 20% EtOAC/Hex, yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.06 (s, 1 H), 7.18-7.13 (m, 2 H), 6.93 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 6.78 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 6.71 (q, *J* = 2.3 Hz, 1 H), 6.20 (t, *J* = 2.4 Hz, 2 H), 5.35 (bs, 1 H), 4.32 (q, *J* = 7.2 Hz, 1 H), 1.68 (d, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.1, 134.9, 131.1, 128.8, 128.2, 121.2, 118.3, 116.8, 108.4, 105.1, 32.2, 19.3. IR 3410, 2970, 1592, 1452, 905, 721 cm^{-1}. HRMS $C_{12}H_{14}NO$ $(M)^+$ calcd. 188.1075, obsvd. 188.1088.

Preparation of 111

The same procedure as that of general procedure was followed except 1 mL of 1-methyl-1*H*-pyrrole was added. C2:C3 alkylation ratio = 4:1, Yield = 52% (average of two run), R_f = 0.50 w/ 20% EtOAC/Hex, yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ =

7.11-7.03 (m, 2 H), 6.85 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 6.74 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1 H), 6.61 (q, *J* = 2.3 Hz, 1 H), 6.20 (ddd, *J* = 3.3 Hz, *J* = 1.9 Hz, *J* = 1.2 Hz, 1 H), 6.15 (t, *J* = 3.2 Hz, 3 H), 5.51 (s, 1 H), 4.20 (q, *J* = 7.2 Hz, 1 H), 3.29 (s, 3 H), 1.65 (d, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 154.2, 135.1, 130.1, 129.2, 128.0, 123.5, 121.0, 117.0, 107.1, 105.8, 34.5, 34.1, 20.1. IR 3369, 2969, 2928, 1594, 1484, 1381, 789 cm^{-1}. HRMS $C_{13}H_{15}NO$ $(M+Na)^+$ calcd. 224.1051, obsvd. 224.1051.

Preparation of 112

The same procedure as that of general procedure was followed except 427.9 mg of 2,5-dimethyl-1*H*-pyrrole was added. Yield = 73% (average of two run), R_f = 0.45 w/ 20% EtOAC/Hex, yellow oil, ^{1}H-NMR (400 MHz, Acetone-D_6) δ = 9.1 (s, 1 H), 7.73 (s, 1 H), 7.13 (dd, *J* = 7.6 Hz, *J* = 1.7 Hz, 1 H), 6.94 (dd, *J* = 7.6 Hz, *J* = 1.7 Hz, 1 H), 6.78-6.70 (m, 2 H), 5.73 (s, 1 H), 4.35 (q, *J* = 7.2 Hz, 1 H), 2.15 (s, 3 H), 1.99 (s, 3 H), 1.44 (d, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, Acetone-D_6) δ = 154.3, 134.8, 128.1, 126.2, 124.2, 122.4, 121.2, 119.6, 115.1, 104.9, 21.5, 12.4, 10.4. IR 3369, 2969, 2928, 1594, 1484, 1381, 789 cm^{-1}. HRMS $C_{14}H_{17}NO$ $(M+Na)^+$ calcd. 238.1208, obsvd. 238.1209.

Preparation of 113

The same procedure as that of general procedure was followed except 787 mg of methyl indolizine-1-carboxylate **(**4.500 mmol, 15.0 equiv.) was added and reaction was heated to 100 °C. Yield = 60% (average of two run), R_f = 0.25 w/ 20% EtOAC/Hex, pale yellow solid, M.P. = 212-214 °C. ^{1}H-NMR (400 MHz, Acetone-D_6) δ = 8.72 (s, 1 H), 8.16 (dd, *J* = 9.1 Hz, *J* = 1.1 Hz, 1 H), 7.87 (d, J = 7.1 Hz, 1 H), 7.11-6.95 (m, 2 H), 6.93 (dd, *J* = 8.0 Hz, *J* = 1.0 Hz, 1 H), 6.74-6.65 (m, 3 H), 4.82 (q, *J* = 7.0 Hz, 1 H), 3.84 (s, 3 H), 1.70 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, Acetone-D_6) δ = 164.7, 154.3,

130.6, 129.5, 128.8, 128.0, 127.7, 127.2, 123.9, 121.8, 120.3, 119.4, 115.4, 113.4, 112.4, 112.2, 50.0, 29.1, 19.6. IR 3243, 2931, 1651, 1526, 1231, 1229, 778 cm^{-1}. HRMS $C_{18}H_{18}NO$ $(M)^+$calcd. 296.1287, obsvd. 296.1291.

Preparation of 114

The same procedure as that of general procedure was followed except 441.0 mg of 2-methoxyfuran was added. Yield = 63% (average of two run), *the product decomposed overtime and gave mixture of unidentified materials.* R_f = 0.55 w/ 20% EtOAC/Hex, yellow oil, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.11-7.05 (m, 2 H), 6.86 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1 H), 6.74 (dd, *J* = 7.9 Hz, *J* = 1.2 Hz, 1 H), 5.92 (d, *J* = 3.2 Hz, 1 H), 5.25 (s, 1 H), 5.02 (d, *J* = 3.2 Hz, 1 H), 4.28 (q, *J* = 7.2 Hz, 1 H), 3.76 (s, 3 H), 1.53 (d, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 161.2, 153.5, 147.9, 129.9, 128.5, 127.8, 121.1, 116.4, 106.5, 79.6, 57.8, 33.5, 18.6. IR 3399, 2950, 1712, 1595, 1451, 1226, 727 cm^{-1}. HRMS $C_{13}H_{14}O_3$ $(M+Na)^+$calcd. 241.0841, obsvd. 241.0849.

Preparation of 115

The same procedure as that of general procedure was followed. Yield = 83% (average of two run), R_f = 0.25 w/ 20% EtOAC/Hex, Sticky oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.03 (s,1 H), 7.35 (dd, *J* = 10.7 Hz, *J* = 8.1 Hz, 2 H), 7.18 (ddd, *J* = 8.1 Hz, *J* = 7.1 Hz, *J* = 1.1 Hz, 1 H), 7.04-6.96 (m, 2 H), 6.79 (td, *J* = 8.4 Hz, *J* = 3.1 Hz, 1 H), 6.68 (dd, *J* = 8.8 Hz, *J* = 4.8 Hz, 1 H), 4.94 (s, 1 H), 4.48 (q, *J* = 7.1 Hz, 1 H), 1.69 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 158.7, 150.1, 137.1, 133.3, 126.6, 122.9, 121.5, 119.9, 119.7, 119.0, 117.3, 114.9, 113.9, 111.5, 32.3, 20.3. IR 3406, 2966, 1617, 1487, 1336, 727 cm^{-1}. HRMS $C_{16}H_{15}NOF$ $(M)^+$ calcd. 256.1138, obsvd. 256.1151.

Preparation of 116

The same procedure as that of general procedure was followed. Yield = 91% (average of two run), R_f = 0.30 w/ 20% EtOAC/Hex, Sticky oil. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.99 (s,1 H), 7.39 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 1 H), 7.18-7.14 (m, 1 H), 7.08 (s, 1 H), 7.01 (t, *J* = 7.5 Hz, 2 H), 6.91 (dd, *J* = 8.0 Hz, *J* = 1.7 Hz, 1 H), 6.65 (d, *J* = 8.0 Hz, 1 H), 4.95 (s, 1 H), 4.46 (q, *J* = 7.1 Hz, 1 H), 2.27 (s, 3 H), 1.71 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 151.9, 137.1, 131.3, 130.1, 129.1, 128.2, 126.9, 122.7, 121.4, 119.9, 119.8, 116.4, 111.4, 32.5, 20.9, 20.5. IR 3406, 2966, 2929, 1617, 1455, 1097, 742 cm^{-1}. HRMS $C_{17}H_{18}NO$ $(M)^+$ calcd. 252.1388, obsvd. 252.1396.

Preparation of 117

The same procedure as that of general procedure was followed. Yield = 90% (average of two run), R_f = 0.30 w/ 20% EtOAC/Hex, M.P. = 105-107 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.05 (s,1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 7.32 (d, *J* = 8.2 Hz, 1 H), 7.20 (t, *J* = 7.6 Hz, 1 H), 7.06 (d, *J* = 8.0 Hz, 1 H), 7.00 (d, *J* = 2.4 Hz, 1 H), 6.92 (d, *J* = 2.7 Hz, 1 H), 6.74-6.71 (m, 2 H), 4.97 (s, 1 H), 4.52 (q, *J* = 7.1 Hz, 1 H), 3.79 (s, 3 H), 1.74 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 153.8, 148.1, 137.0, 133.0, 126.7, 122.7, 121.4, 119.8, 119.7, 119.4, 117.0, 114.7, 111.9, 111.4, 55.8, 32.5, 20.4. IR 3413, 3311, 2973, 1506, 1456, 1097, 810, 738 cm^{-1}. HRMS $C_{17}H_{18}NO_2$ $(M)^+$ calcd. 268.1338, obsvd. 268.1342.

Preparation of 118

The same procedure as that of general procedure was followed. Yield = 61% (average of two run), R_f = 0.30 w/ 20% EtOAC/Hex, pale green solid, M.P. = 94-96 °C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.98 (s,1 H), 7.40 (dd, *J* = 8.0 Hz, *J* = 0.6 Hz, 1 H), 7.32 (dt, *J* = 8.0 Hz, *J* = 0.8 Hz, 1 H), 7.20-7.17 (m, 2 H), 7.04-7.00 (m, 3 H), 6.86 (t, *J* = 7.5 Hz, 1 H), 5.23 (s, 1 H), 4.49 (q, *J* = 7.1 Hz, 1 H), 2.17 (s, 3 H), 1.74 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 152.7, 137.2, 131.0, 129.3, 126.8, 126.2, 125.0, 122.8, 121.5, 120.5, 120.0, 119.9, 119.7, 111.5, 33.0, 20.5, 16.1. IR 3406, 2966, 2929, 1617, 1455, 1097, 742 cm^{-1}. HRMS $C_{17}H_{17}NO$ $(M+Na)^+$ calcd. 274.1208, obsvd. 274.1212.

Preparation of 119

The same procedure as that of general procedure was followed. Yield = 38% (average of two run), R_f = 0.28 w/ 20% EtOAC/Hex, pale green solid, M.P. = 145-147 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.91 (s,1 H), 7.35-7.30 (m, 2 H), 7.15-7.11 (m, 3 H), 7.01-6.96 (m, 2 H), 6.71-6.69 (m, 2 H), 4.66 (s, 1 H), 4.29 (q, *J* = 7.1 Hz, 1 H), 1.65 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 153.7, 139.4, 136.9, 128.8, 128.7, 127.1, 122.1, 121.9, 121.2, 120.0, 119.3, 115.3, 111.2, 36.3, 22.7. IR 3415, 2963, 1611, 1510, 1455, 1222, 745 cm^{-1}. HRMS $C_{16}H_{15}NO$ $(M+Na)^+$ calcd. 260.1051, obsvd. 260.1065.

Accessing Interesting Indole Core Structure

Synthesis of Triflate (S2)

In a dry round bottom flask 200 mg (0.85 mmol, 1.0 equiv.) of **101** was dissolved in 8.0 mL of DCM. To this 135 µL (1.27 mmol, 1.5 equiv.) of 2,6-lutidine was added and the reaction mixture was cooled to -78 °C. At this temperature 213 µL (1.27 mmol, 1.5 equiv.) of Tf_2O was added drop wise. The reaction mixture was allowed to stir for 1 h at -78 °C and slowly warmed to room temperature. On completion, reaction mixture

was quenched with water. The organic phase was diluted with 5 mL of DCM and washed with water (10 mL x 2) followed by brine (10 mL) wash. The organic layer was dried on Na_2SO_4 and concentrated in vacuo. The crude mixture was passed through small silica plug with DCM as eluent and was taken forward without further purification.

Synthesis of 121

In the glovebox, to a 2.5 dram vial equipped with a stir bar was added 32.1 mg Pd_2dba_3 (0.035 mmol, 0.1 equiv.), 30.0 mg dppb (0.070 mmol, 0.2 equiv.) and 1.0 mL of DMA. The reaction mixture was allowed to stir for ca.15 min. In a separate 2.5 mL dram vial equipped with a stir bar was added 130.0 mg of **S2** (0.35 mmol, 1.0 equiv.) and 343.0 mg of KOAc (3.50 mmol, 10.0 equiv.) in 2.5 mL of DMA. To this, catalyst solution was added. The vial was capped and was heated to 100 °C for 8 h, in oil bath, and diluted with 3 mL of EtOAc. The reaction mixture was then passed through silica gel to remove metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography to give product in 87% isolated yield.

The ^{1}H-NMR spectrum of product was matched with literature.[34]

Synthesis of 122

In a dry round bottom flask 28 mg (0.020 mmol, 0.10 equiv.) of $Pd(OH)_2/C$ was taken and 1 mL of EtOAc was added. To this a solution of 74 mg (0.20 mmol, 1.0 equiv.) of triflate in 3 mL of MeOH was added followed by addition of 110 µL of TEA (1.0 mmol, 5.0 equiv.). The flask was evacuated and refilled three times with hydrogen balloon. The reaction was allowed to stir for 3 h. On completion, reaction mixture was passed though silica plug to give desired product in 87% isolated yield.

The ^{1}H-NMR spectrum of product was matched with literature.[50]

Synthesis of 123

In a dry round bottom flask 60 mg (0.25 mmol, 1.0 equiv.) of **101** was dissolved in 2.0 mL of DCM. To this 70 mg (0.28 mmol, 1.1 equiv.) of PPTS was added and the reaction mixture was cooled to -78 °C. At this temperature, a solution of 50 mg (0.28 mmol, 1.1 equiv.) of NBS in 2.0 mL of THF was added dropwise. The reaction mixture was allowed to stir for 45 min at -78 °C and quenched with 2 mL of $NaHCO_3$. The organic phase was diluted with 5 mL of DCM and washed with water (10 mL X 2) followed by brine (10 mL) wash. The organic layer was dried on Na_2SO_4 and concentrated in vacuo. The crude mixture was purified by silica gel column chromatography with 2% to 10% EtOAc:Hex as eluent to give desired product in 80% yield. R_f = 0.56 w/ 20% EtOAC/Hex, yellow solid, M.P. = 114-120 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.76 (s, 1 H), 7.50-7.48 (m, 1 H), 7.35-7.31 (m, 1 H), 7.28-7.19 (m, 2 H), 7.14-7.10 (m, 3 H), 7.01-7.04 (m, 1 H), 4.41 (q, *J* = 6.8 Hz, 1 H), 1.68 (d, *J* = 6.8 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 150.8, 140.2, 131.1, 129.9, 127.6, 127.0, 126.4, 124.1, 123.2, 120.5, 120.3, 117.8, 117.0, 110.8, 29.3, 24.8. IR 2963, 1718, 1616, 1599, 1455, 1369, 746 cm^{-1}. HRMS $C_{16}H_{13}NO$ $(M)^+$ calcd. 235.0997, obsvd. 235.0996.

Inverse Electron Demand Diels-Alder Reaction

In the glovebox, to a 2.5 dram vial equipped with a stir bar was added 14.1 mg Pd_2dba_3 (0.015 mmol, 0.050 equiv.), 15.0 mg $P(Cy)_3$ (0.051 mmol, 0.17 equiv.) and 1.0 mL of toluene. The reaction mixture was allowed to stir for *ca.*15 min. In a separate 25 mL sealed flask equipped with a stir bar was added 165.0 μL of C_4H_9Cl (1.80 mmol, 6.0 equiv.), 30.0 mg of $KHCO_3$ (0.30 mmol, 1.0 equiv.) and 761.5 mg of *tert*-butyl 2,3-dihydro-1*H*-pyrrole-1-carboxylate (4.500 mmol, 15.0 equiv.) and 36.0 mg of **18** (0.30

mmol, 1.00 equiv.) in 2.0 mL of toluene. To this catalyst solution was added. The flask was capped and was heated to 100 °C for 72 h, in oil bath, and diluted with 10 mL of EtOAc. The reaction mixture was then passed through silica gel to remove metal complexes and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Yield = 63% (average of two run), R_f= 0.42 w/ 20% EtOAC/Hex, Sticky Oil, ^{1}H-NMR (400 MHz, Benzene-D_6, 70 °C) δ = 6.93-6.90 (m, 2 H), 6.82 (dd, *J* = 8.4 Hz, *J* = 1.1 Hz, 1 H), 6.74 (t, *J* = 7.4 Hz, 1 H), 5.69 (s, 1 H), 3.35-2.95 (m, 4 H), 2.71 (quintet, *J* = 6.8 Hz, 1 H), 1.83-1.75 (m, 1 H), 1.44 (s, 9 H), 0.89 (d, *J* = 6.8 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 152.7, 126.0, 125.6, 120.8, 116.9, 86.0, 79.3, 45.0, 43.7, 28.4, 22.3, 15.7. IR 2973, 1701, 1455, 1391, 1168, 754 cm^{-1}. HRMS $C_{17}H_{23}O_3N$ $(M+Na)^+$ calcd. 312.1576, obsvd. 312.1574.

Control Experiments (Figure 4.11)

Reaction A

In the glovebox, to a 2.5 dram vial equipped with a stir bar were added 4.7 mg Pd_2dba_3 (0.005 mmol, 0.050 equiv.), 5.0 mg $P(Cy)_3$ (0.017 mmol, 0.17 equiv.) and 500 µL of toluene. The reaction mixture was allowed to stir for ca.15 min. In a separate 2.5 dram vial equipped with a stir bar was added 10.0 mg of $KHCO_3$ (0.10 mmol, 1.0 equiv.) and 217.5 mg of 1,2-dimethylindole (1.500 mmol, 15.0 equiv.) and 12.0 mg of **18** (0.10 mmol, 1.00 equiv.) in 500 µL of toluene. To this catalyst solution was added. The flask was capped and was heated to 80 °C for 72 h, in oil bath, and diluted with 3 mL of EtOAc. The reaction mixture was then passed through silica gel and concentrated *in vacuo*. The crude mixture was purified with flash silica-gel column chromatography.

Reaction B

To a 2.5 dram vial equipped with a stir bar were added 217.5 mg of 1,2-dimethylindole (1.500 mmol, 15.0 equiv.) and 12.0 mg of **18** (0.10 mmol, 1.00 equiv.) in 1.0 mL of toluene. After purging with N_2, the flask was capped and was heated to 80 °C for 72 h, in oil bath, and diluted with 3 mL of EtOAc. The reaction mixture was then passed through silica gel and concentrated in vacuo. The crude mixture was purified with flash silica-gel column chromatography.

Deuterium Labeling Experiments

For these reactions (Figure 4.12) the same procedure as the general procedure was followed. Except for reaction A, OD-phenol (**124**) was used, whereas for reaction B, OD-phenol **(124)** and C_4D_9Br were used.

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CHAPTER 5

ACID-CATALYZED HYDROFUNCTIONALIZATION OF VINYL INDOLES: AN EFFICIENT METHOD TO SYNTHESIZE BISINDOLYLMETHANES

Introduction

Bisindolylmethane (BIM) scaffolds are present in many natural products isolated from terrestrial and marine natural sources.[1] These natural products exhibit various biological activities, including anti-cancer activity against multiple cancer cell-lines.[2] Naturally occurring bisindolylmethane, such as Vibrindole A (**127**), is useful in the treatment of fibromyalgia, chronic fatigue, and irritable bowel syndrome.[3-5] Diindolylmethane **128** inhibits the proliferation of both estrogen-dependent and independent cultured breast tumor cells (Figure 5.1).[6-8] Additionally, synthetic bisindolylmethanes are important pharmacophores with various biological activities,[9-12] and they recently have found use in material chemistry.[13-15] Because of their extensive utility, numerous methods are available to synthesize symmetrical BIMs.[1] Nevertheless, the efficient synthesis of unsymmetrical BIMs is still a challenge. Because of this limitation and our recent discovery of Pd-hydride chemistry (discussed in Chapter 4), we became interested in developing Pd-catalyzed hydrofunctionalization of vinyl indoles to provide unsymmetrical bisindolylmethanes.

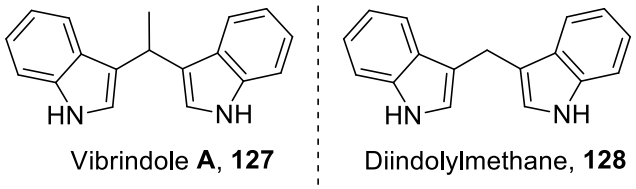


Figure 5.1. Examples of biologically relevant bisindolylmethanes.

Background

Bisindolylmethanes are a highly important molecular scaffold in the pharmaceutical industry.[1] Thus, various groups have reported the synthesis of unsymmetrical bisindolylmethanes in recent years. Most of these examples follow a leaving group strategy as shown in Figure 5.2.[15] Herein, some of the recent developments are presented.[16-19]

In 2005, Ji and coworkers reported the synthesis of unsymmetrical bisindolylmethanes catalyzed by ceric ammonium nitrate (CAN) (Figure 5.3).[20] The reaction of indoles with derivatives of (1*H*-indol-3-yl) methanol , in the presence of 10 mol% CAN, gave the desired products in excellent yield. The reaction is proposed to proceed via alkylideneindoleninium intermediate **A.**

In 2006, Tse and coworkers reported a similar method for the preparation of unsymmetrical bisindolylmethanes (Figure 5.4).[16-17] In this chemistry, the authors used silica as a mild acid to promote the formation of the key cationic alkylideneindoleninium intermediate, which reacts with an equivalent of indole to give the desired product. In this report, alcohol **131** and aziridine precursor **129** were used as key substrates for the preparation of potentially pharmacologically active bisindoles **132** and **130** in good to excellent yields. This method's key feature is the absence of organic solvent. The reaction in the case of substrate **131** was thought to proceed via formation of alkene **133**

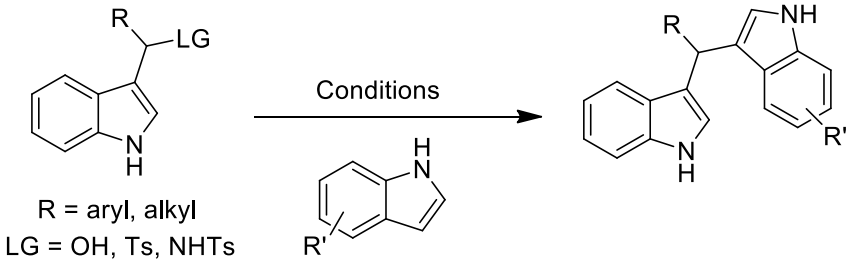


Figure 5.2. Common strategy to synthesize unsymmetrical bisindolylmethanes.

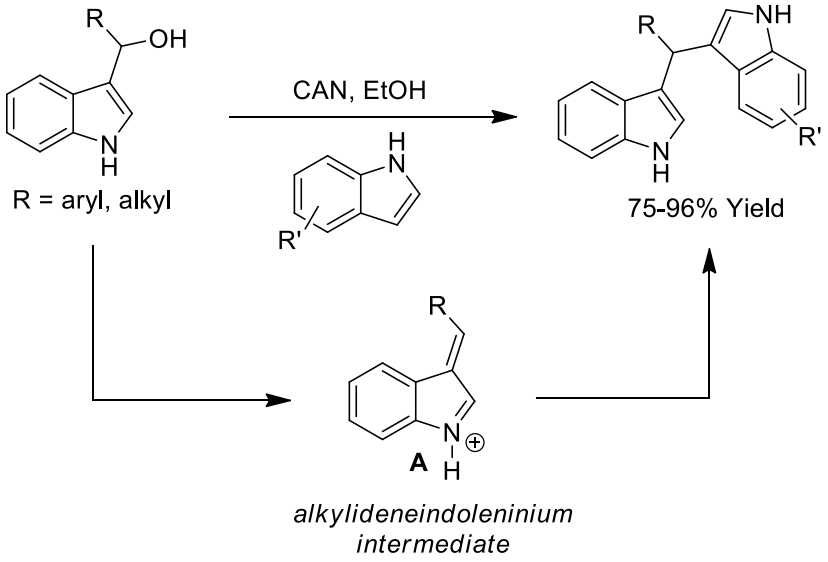


Figure 5.3. Synthesis of unsymmetrical bisindolylmethanes catalyzed by ceric ammonium nitrate. Data from Ji and coworkers.

in situ. However, when alkene **133** was reacted with a catalytic amount of methylsulfonic acid (MsOH), with DCM as a solvent, no product formation was observed. Based on this observation, the authors ruled out in situ alkene generation from alcohol substrate **131**. Later, they expanded the scope of this process to include other nucleophiles.

In the same year, Csaky and coworkers reported Ir^{I}- or Rh^{I}-catalyzed formation of

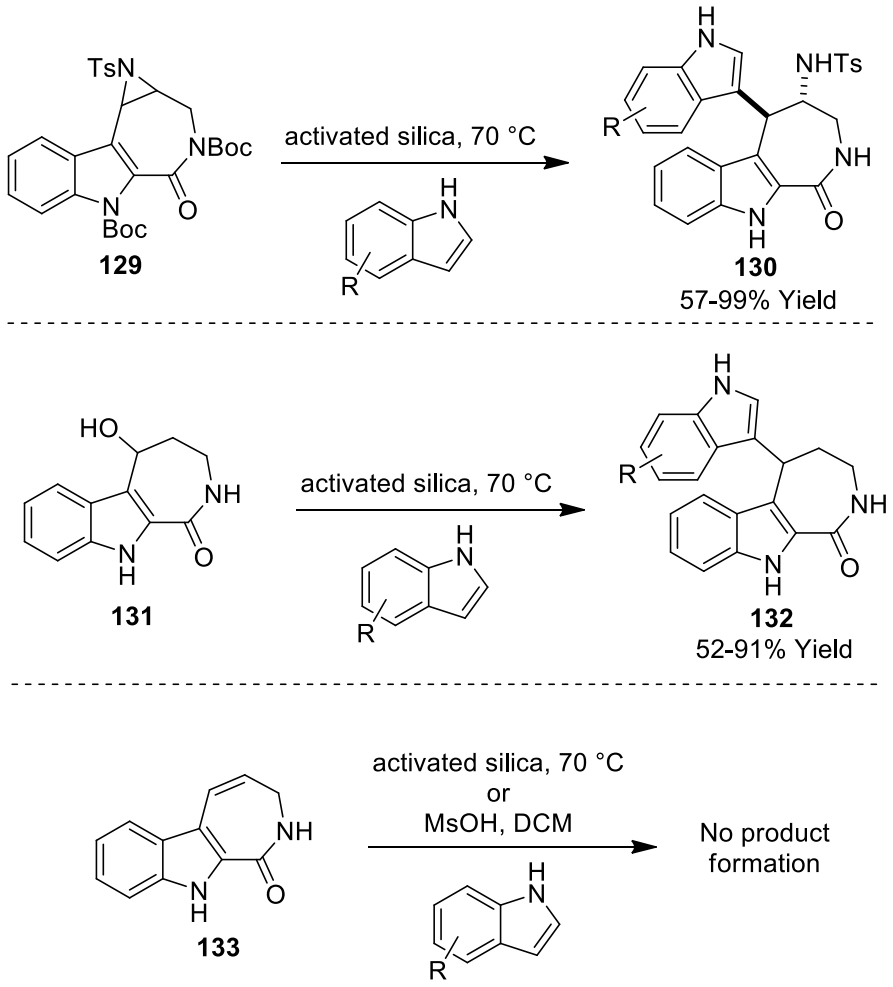


Figure 5.4. Silica gel catalyzed, solvent free synthesis of unsymmetrical bisindolylmethanes. Data from Tse and coworkers.

bisindolylmethanes (Figure 5.5).[21] Treating readily available gramine derivatives with indoles in the presence of Rh^{I}-catalyzed gave the desired bisindoles in good yields. Because this reaction can be performed in aqueous media, this method is attractive for manufacturing processes. The proposed mechanism of product formation is shown in Figure 5.5b, where coordination of Rh^{I} with nitrogen followed by base promoted elimination leads to intermediate A. Intermediate **A** converts to intermediate **B**, which

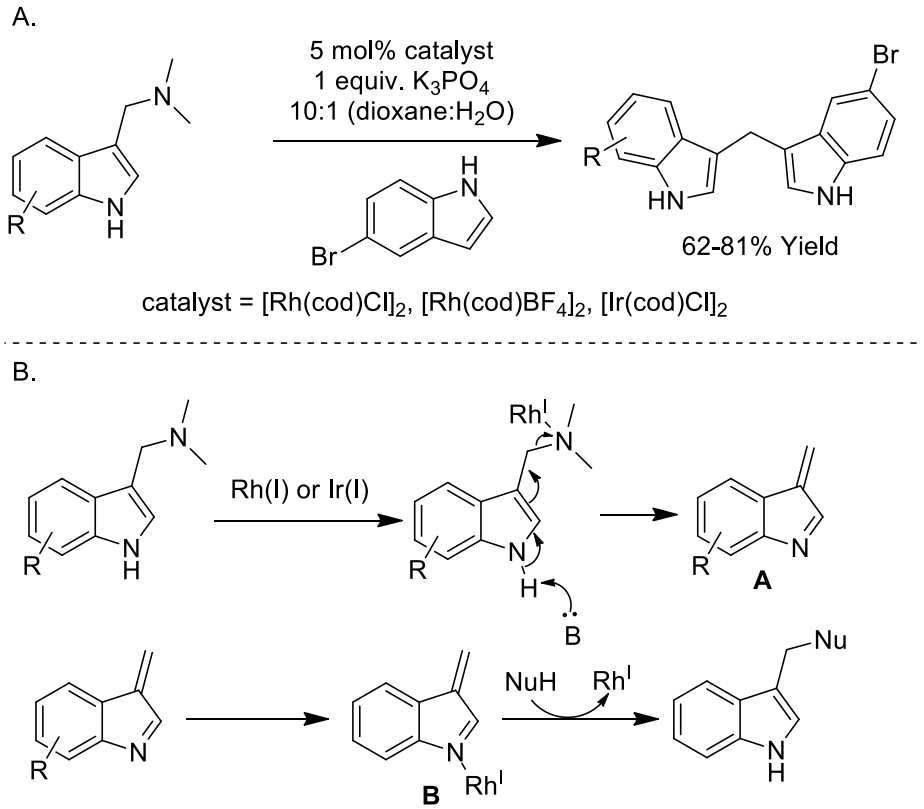


Figure 5.5. Rh/Ir-catalyzed formation of BIMs. Data from Csaky and coworkers.

reacts with exogenous indole to give the desired product.

In 2008, Palmisano and coworkers reported a three-component, one-pot domino reaction that combines the allylindation of 1*H*-indole-3-carbaldehyde with the dehydrative alkylation of heterocycles (Figure 5.6).[22] The scope of this process is broad in both reaction partners. However, only allylindium is used as the initiator of the domino process. The proposed reaction mechanism is shown in Figure 5.6b, the initial reaction of allyindium with 1*H*-indole-3-carbaldehyde gives *sec*-alcohol **134** as the product. The subsequent indium-catalyzed dehydration of **134** followed by Friedel–Crafts type alkylation, leads to product formation.

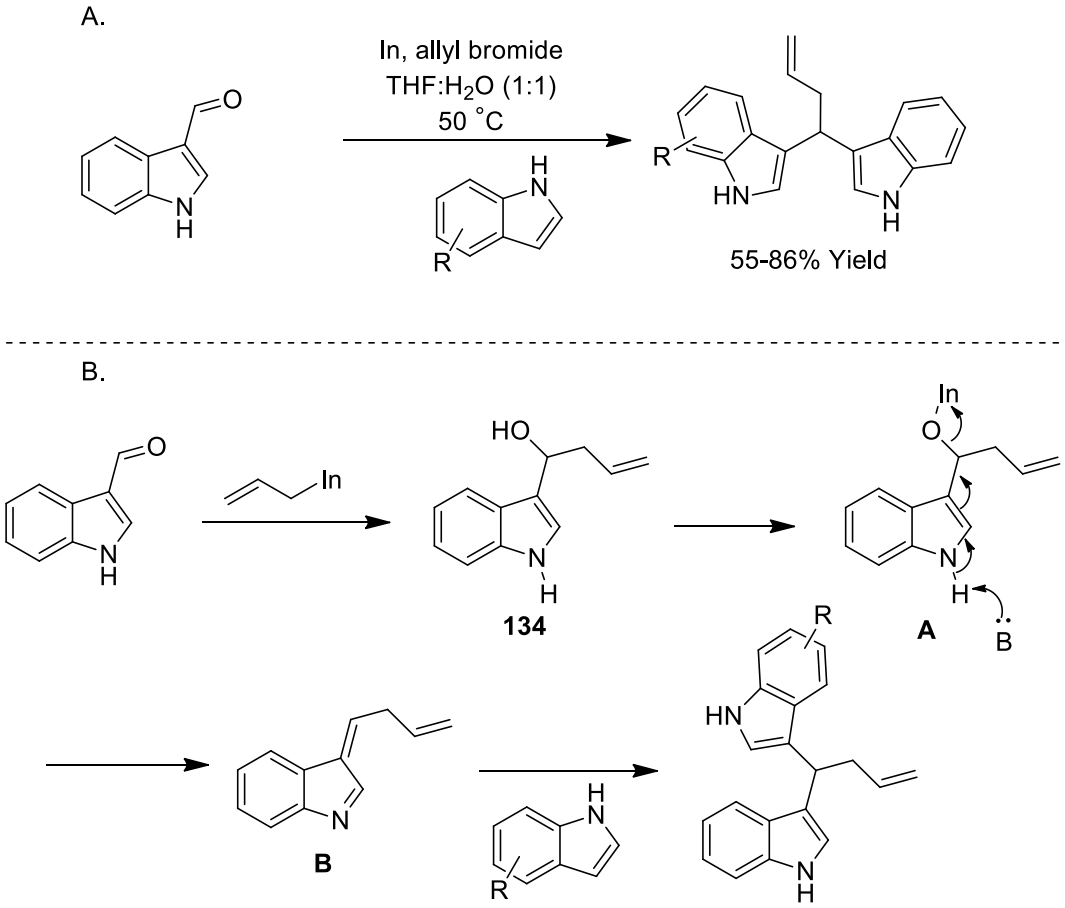


Figure 5.6. A three-component, one-pot domino reaction to synthesize bisindoles. Data from Palmisano and coworkers.

In 2010, You and coworkers reported the first enantioselective preparation of bisindolylmethanes (Figure 5.7).[18] Chiral phosphoric acids were used as the Brønsted acid catalyst for reacting amine **135** and indoles. The presence of an arene at the benzylic position of indole **135** is necessary for stabilization of proposed cationic indoleninium intermediate, which limits the scope significantly. Moreover, bisindolylmethanes can only be obtained in low ee.

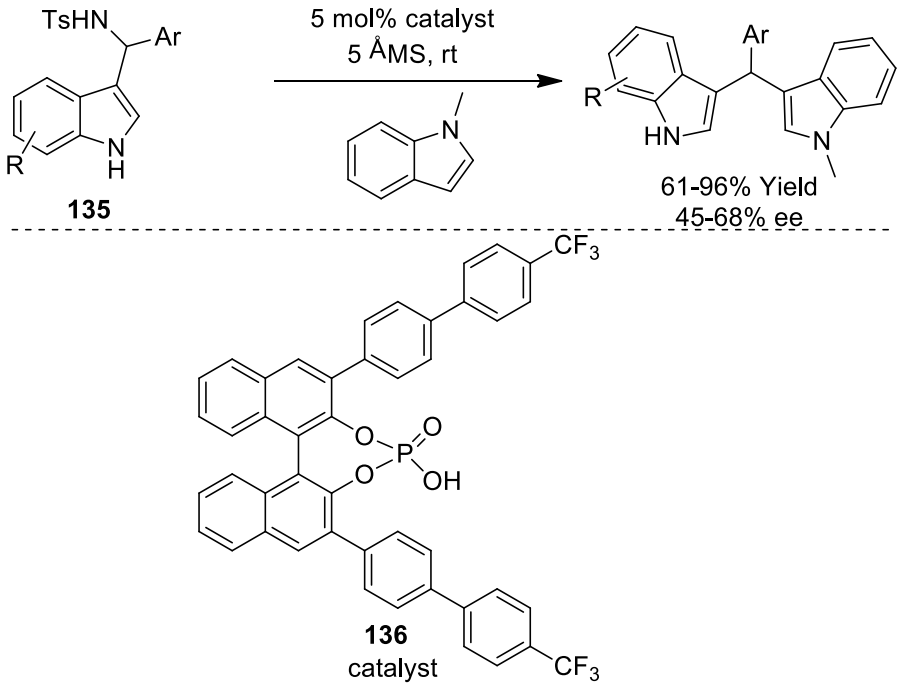


Figure 5.7. Chiral Brønsted acid catalyzed enantioselective preparation of bisindolylmethanes. Data from You and coworkers.

As discussed above, various methods are available for synthesizing unsymmetrical bisindolylmethanes. However, an efficient and simple method of constructing bisindolylmethanes, with broad substrate scope, has not been reported. Besides, our approach to access bisindolylmethanes via alkene hydrofuncationalization would provide a mechanistically distinct route to these biologically relevant scaffolds.

Approach

With our recent success in the development of a Pd^0-catalyzed hydrofunctionalization of vinyl phenols, we choose to utilize a similar concept to synthesize unsymmetrical bisindolylmethanes from vinyl indoles. The mechanistic proposal is shown in Figure 5.8, initiates with the oxidative addition of an alkyl halide resulting in Pd-alkyl intermediate **A**. Subsequent β-hydride elimination of **A** would

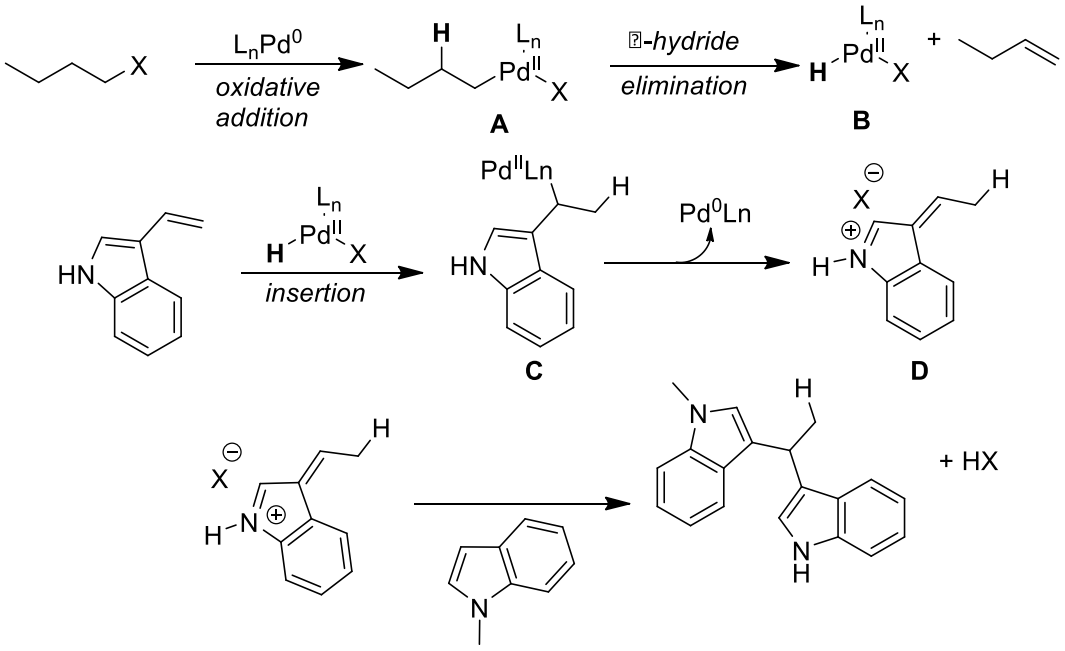


Figure 5.8. Proposed mechanism.

provide the requisite Pd-hydride **B**. Insertion of an alkene in the Pd-hydride **B** followed by reduction of Pd^{II} to Pd^{0} would lead to the key intermediate **D**. Nucleophilic attack of the indole on intermediate **D** followed by re-aromatization of indole would lead to formation of the desired product. This approach would provide a mechanistically distinct method for accessing biologically relevant bisindolylmethanes.

Reaction Optimization and Scope

Reaction optimization and evaluation of substrate scope was conducted in collaboration with German exchange student Mr. Jaroslaw Osiak.

The reaction of **137** under previously optimized reaction conditions (Chapter 4) resulted in no desired product formation (Figure 5.9). We believe this could be due to poor binding of an alkene with an electron rich Pd-catalyst. To increase the binding efficacy of alkenes with the Pd-catalyst, a cationic Pd complex was desired. Based on findings reported by former group member Dr. Kaveri Balan, where use of cationic Pd-complex had a significant impact on reaction outcome, alkyl tosylate as a sacrificial hydride source, DMA as a solvent, and I*i*Pr-carbene as a ligand were used. Excitingly, under this new set of conditions, 82% yield of the desired product was observed. Because, 1 equivalent of *p*-TsOH (related to Pd) was generated at the end of every catalytic cycle (see Figure 5.8) and the lack of base to neutralize generated acid in reaction conditions; a control reaction with 20 mol% *p*-TsOH was conducted to probe for Brønsted acid-catalyzed pathways. Interestingly, 82% yield of the desired product was observed suggesting that *p*-TsOH could be an active catalyst under the Pd-catalyst conditions. Since, a simple Brønsted acid provided the desired product in excellent yield, it was chosen as the preferred catalyst for further optimization.

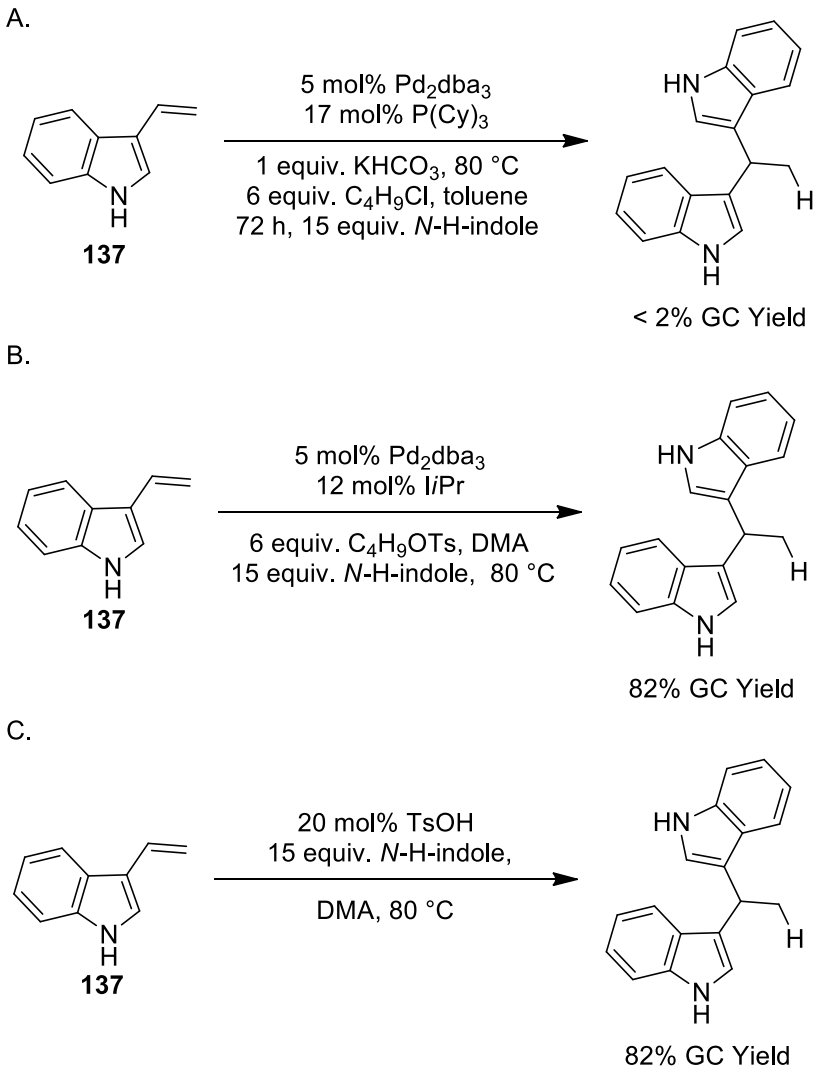
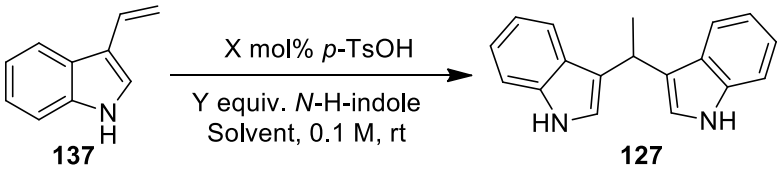


Figure 5.9. Initial optimization of the reaction conditions.

When **137** was treated with 20 mol% of *p*-TsOH in either dichloromethane (DCM), dichloroethane (DCE) or toluene, complete conversion of **137** was observed within a few hours with <10% yield of the desired product and poor mass balance (Table 5.1, entries 1-3). This observation alludes to the tendency of substrate **137** to polymerize under acidic conditions. In Lewis basic DMA, we have observed good yield of the desired product, even at elevated temperature . Thus, a reaction at room temperature

Table 5.1. Reaction optimization.



137 **127**

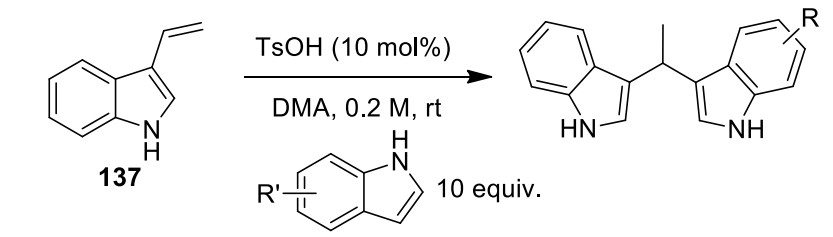
Entry	X	Y	Solvent	t (h)	% Conv.[a]	% **127**[a]
1	20	15	DCM	2	>99	<5
2	20	15	DCE	2	>99	<5
3	20	15	toluene	2	>99	9
4	20	15	DMA	16	>99	89
5[b]	10	7	DMA	16	>99	73[c]
6[b]	**10**	**10**	**DMA**	**16**	**>99**	**81[c]**

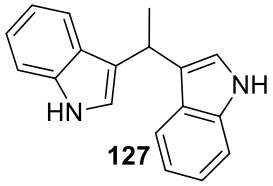
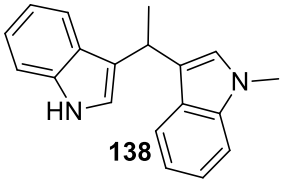
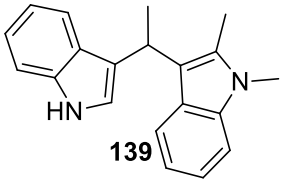
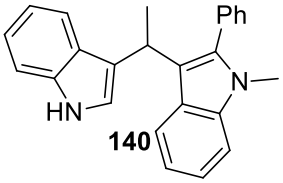
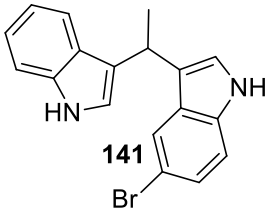
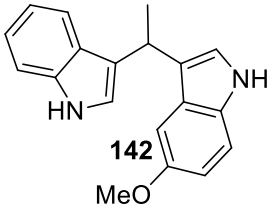
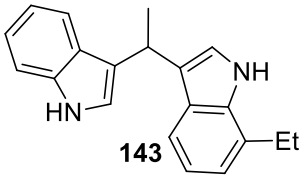
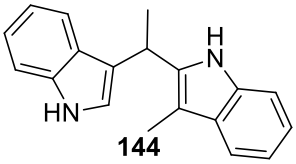
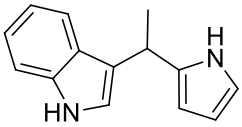
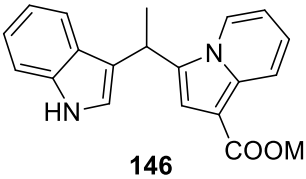
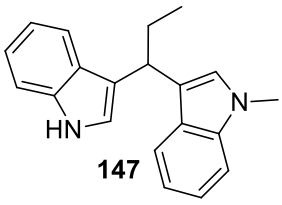
a) The conversion and yield were measured by GC with an internal standard. b) Concentration of the reaction mixture (with respect to **137**): 0.2 M c) Isolated yield.

in DMA was performed to give the desired product in 89% GC yield (Table 5.1, entry 4). Further optimization of acid and nucleophile loadings gave the optimal conditions, in which 81% isolated yield of the desired product was obtained (Table 5.1, compare entries 4, 5 and 6).

With this optimized system in hand, the scope of exogenous nucleophiles was explored. The unprotected 1*H*-indole as a nucleophile gave the natural product Vibrindole **A** in 80% isolated yield without the exclusion of air or moisture from the system with >90% recovery of the remaining nucleophile (Table 5.2, compound **127**). *N*-methyl indole also gave the corresponding 3,3'-bisindolylmethane in good yield (Table 5.2, compound **138**). Furthermore, various substitution on the indole ring is well

Table 5.2. Scope of exogenous nucleophiles with substrate **137**.



 **127**	 **138**	 **139**
8 h, 80% Yield	8 h, 81% Yield	8 h, 85% Yield
 **140**	 **141**	 **142**
16 h, 55% Yield	12 h, 42% Yield	16 h, 73% Yield
 **143**	 **144**	 **145**
16 h, 62% Yield	16 h, 54% Yield[b]	16 h, 55% Yield
 **146**	 **147**	
16 h, 68% Yield	16 h, 84% Yield[b]	

a) Yields are averages of at least two runs at 0.3 mmol scale.
b) Reactions were performed at 70 °C.

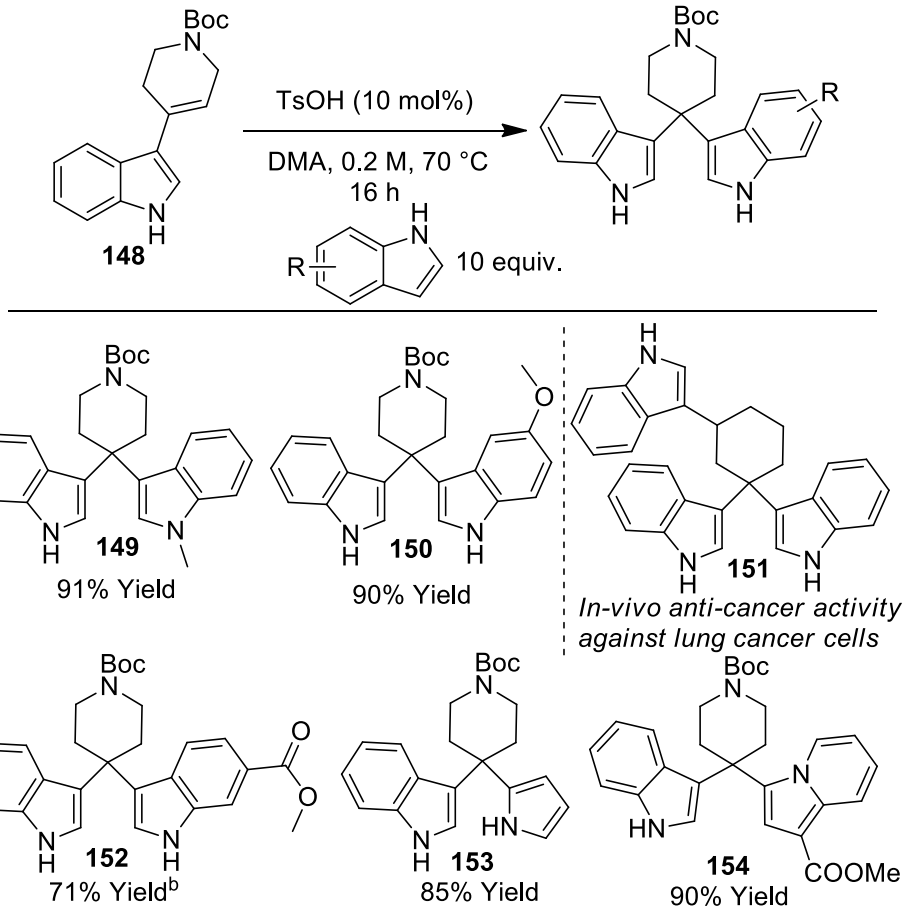
tolerated under the reaction conditions including sterically demanding 2-substituted indoles (Table 5.2, compounds **139-143**). The 2,3'-bisindolylmethanes can also be obtained using this method, as demonstrated by the successful use of 3-methyl indole to give the desired product in good yield albeit higher reaction temperature was required (Table 5.2, compound **144**). A pyrrole and an indolizine can also be used as nucleophile to provide the corresponding bis-heteroarylmethanes in good yields (Table 5.2, compounds **145** and **146**). Additionally, a disubstituted vinylindole gave the desired product in 84% yield (Table 5.2, compound **147**).

Encouraged by these results, trisubstituted vinyl indole **148** was prepared in high yield by condensation of indole with the corresponding cyclic ketone.[23] As expected, the substrate **148** underwent a smooth hydrofunctionalization reaction with the exogenous nucleophile, *N*-Me-indole, to give the desired product in excellent yield (Table 5.3, compound **149**). The BIM obtained (**149**) is chemically intriguing with its one all-substituted carbon center. Moreover, it is also biologically intriguing due to its similarity to BIM **151**, which shows interesting in vivo activity against lung cancer cells.[24] Additionally, both electron-rich and electron-deficient indoles are well tolerated under the reaction conditions (Table 5.3, compounds **150** and **152**). Both a pyrrole and an indolizine as exogenous nucleophiles gave the desired products in good yields (Table 5.3, compounds **153-154**).

Biological Study

In light of the previously established biological activity of diindolylmethane (**128**) against a breast cancer cell line[25-27] and our recent discovery of cytotoxic indole containing compounds (as discussed in Chapter 3), the biological activity of the newly

Table 5.3. Scope of exogenous nucleophiles with substrate **148**.



a) Yields are averages of at least two runs at 0.2 mmol scale.
b) Reaction time = 30 h.

synthesized bisindolylmethanes was probed in the MCF-7 breast cancer cell line. These studies were conducted by Ms. Rachel Vaden. Interestingly, several compounds, including compounds **139** and **149,** were found to reduce cell count in comparison to the DMSO control in MCF-7 cell lines (Figure 5.10). Excitingly, compound **149** displays excellent differential activity between MCF-7 and MCF-10A (normal breast) cells. Even at the highest concentration evaluated (100 μM) **149** does not generally affect the growth of MCF-10A cells whereas it leads to an EC_{50} of 4.3 μM in MCF-7 cells (Figure 5.10). Additionally, compound **154** demonstrated an EC_{50} of ~50 *n*M although no selectivity for either cell line is observed (Figure 5.11).

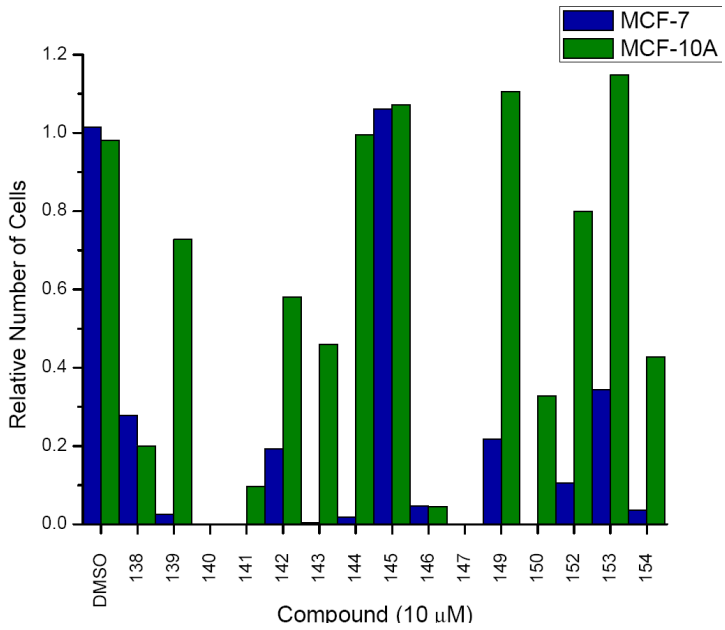


Figure 5.10. Evaluation of biological activities of newly synthesized BIMs in MCF-7 cell lines.

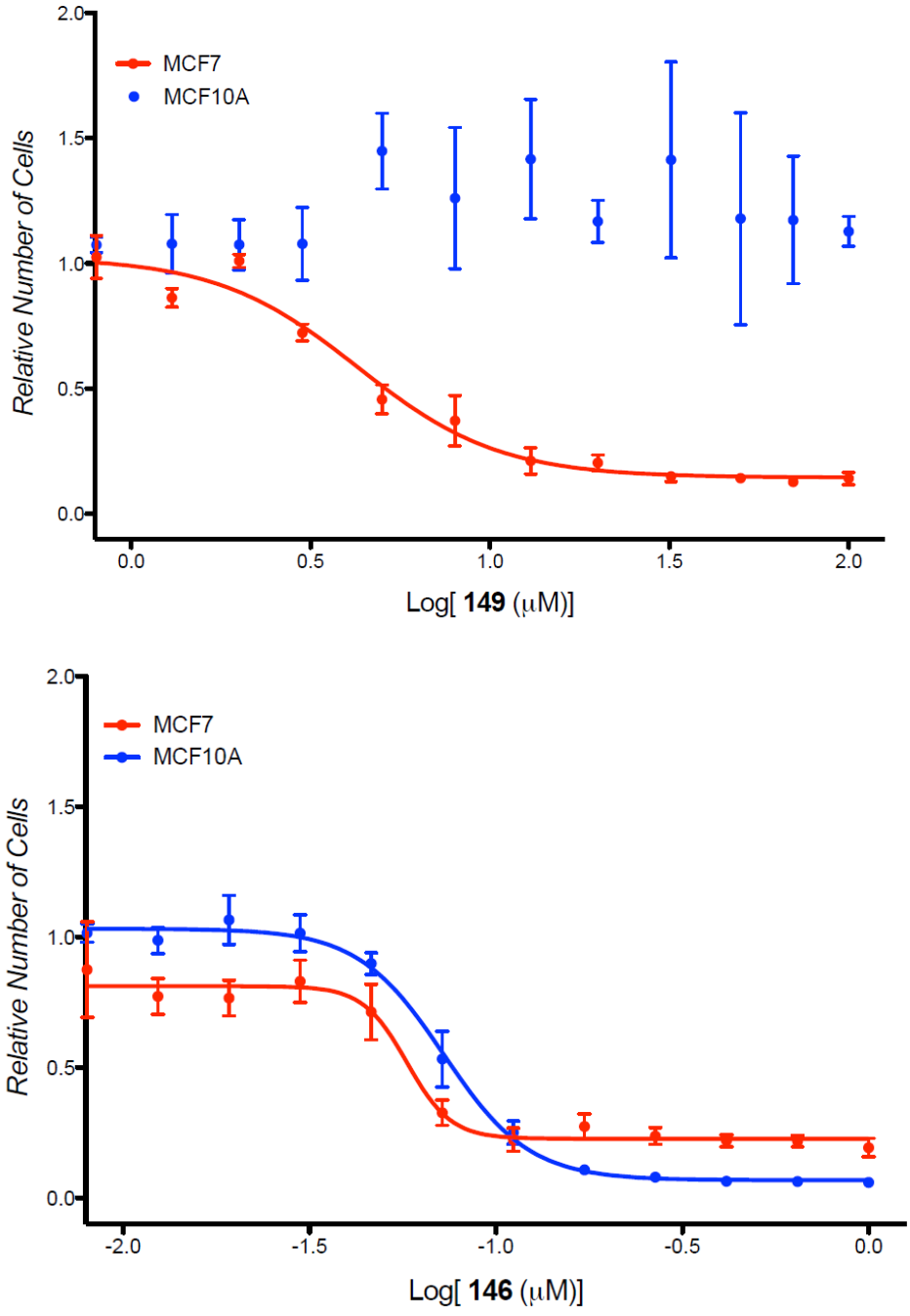


Figure 5.11. Dose response curves for compounds **149** and **146**.

Conclusion

A simple and efficient reaction to access biologically relevant bisindolylmethanes from vinyl indoles has been reported. This method offers a distinct alternative to access alkylideneindoleninium intermediates in situ,[29] which could be subjected to the reaction of various nucleophiles providing functionalized indoles. Broad scope and ease of the reaction highlight this method. Future work is focused on the further evaluation of analogs of compound **149,** as well as identification of its biological target.

Experimental

General Information

Toluene, dichloromethane, and THF were dried before use by passing through a column of activated alumina. All other reagents (including indoles) were purchased from commercial sources and used without further purification. Yields were calculated for material judged homogeneous by thin-layer chromatography and NMR. Thin-layer chromatography was performed with EMD silica gel 60 F254 plates eluting with the solvents indicated, visualized by a 254 nm UV lamp, and stained either with potassium permanganate, *p*-anisaldehyde, phosphomolybdic acid or vanillin. Flash column chromatography was performed with EcoChrom MP Silitech 32-63D 60Å silica gel, slurry packed with solvents indicated in glass columns. Nuclear magnetic resonance spectra were acquired at 400 MHz for ^{1}H, and 100 MHz for ^{13}C. Chemical shifts for proton nuclear magnetic resonance (^{1}H NMR) spectra are reported in parts per million downfield relative to the line of $CHCl_3$ singlet at 7.26 ppm. Chemical shifts for carbon nuclear magnetic resonance (^{13}C NMR) spectra are reported in parts per million downfield relative to the center-line of the $CDCl_3$ triplet at 77.2 ppm. The abbreviations s,

d, t, q, td, dd and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, triplet of doublet, doublet of doublet and multiplet, respectively. IR spectra were recorded using a Nicolate FT-IR instrument. Glassware for all reactions was oven-dried at 110 ^{o}C and cooled while purging with nitrogen prior to use.

Substrate Synthesis

Substrate **137** was synthesized using literature procedure.[28] *^{1}H-NMR was matched with literature ^{1}H-NMR for all substrates. Note: Substrates were stored at -28 °C in dark.*

Procedure for Optimization

Figure 5.9, Reaction A

In the glovebox, to a 2.5 dram vial equipped with a stir bar were added 4.7 mg Pd_2dba_3 (0.0050 mmol, 0.050 equiv.), 5.6 mg $P(Cy)_3$ (0.020 mmol, 0.20 equiv.) and 200 μL of toluene. The reaction mixture was allowed to stir for ca.15 min. In a separate 2.5 dram vial equipped with a stir bar were added 165 μL of butyl chloride (0.06 mmol, 6.0 equiv.), 10.0 mg of $KHCO_3$ (0.10 mmol, 1.0 equiv.), 175.5 mg of *N*-H-dimethylindole (1.500 mmol, 15.00 equiv.) and 200 μL of standard solution of **137** (0.10 mmol, 1.00 equiv.) in toluene (*standard solution*: 21.5 mg of **137**, and 10 μL of undecane as internal standard in 300 μL of toluene). To this an additional 600 μL of toluene and the catalyst solution were added. The vial was capped and was heated to 80 °C for 72 h in an oil bath. At this point the vial was open to air and the reaction was analyzed by GC using an internal standard to calculate conversion as well as yield of various products.

Figure 5.9, Reaction B

In the glovebox, to a 2.5 dram vial equipped with a stir bar were added 4.7 mg Pd_2dba_3 (0.0050 mmol, 0.050 equiv.), 5.0 mg I*i*Prcarbene (0.010 mmol, 0.10 equiv.) and 200 μL of DMA. The reaction mixture was allowed to stir for ca.15 min. In a separate 2.5 dram vial equipped with a stir bar were added 70 mg of butyl chloride (0.03 mmol, 3.0 equiv.), 175.5 mg of *N*-H-dimethylindole (1.500 mmol, 15.00 equiv.) and 200 μL of standard solution of **137** (0.10 mmol, 1.00 equiv.) in DMA (*standard solution*: 21.5 mg of **137**, and 10 μL of undecane as internal standard in 300 μL of DMA). To this an additional 600 μL of DMA and the catalyst solution were added. The vial was capped and was heated to 80 °C for 16 h in an oil bath. At this point the vial was open to air and the reaction was analyzed by GC using an internal standard to calculate conversion as well as yield of various products.

Figure 5.9, Reaction C

To a 2.5 dram vial equipped with a stir bar were added 3.44 mg *p*-TsOH (0.0200 mmol, 0.200 equiv.), 175.5 mg of *N*-H-indole (1.500 mmol, 15.00 equiv.) and 200 μL of standard solution of **137** (0.100 mmol, 1.00 equiv.) (*standard solution*: 21.5 mg of **137**, and 10 μL of undecane as internal standard in 300 μL of toluene). To this an additional 800 μL of toluene was added. The vial was capped and was stirred for 2 h at 80 °C. At this point reaction was analyzed by GC using an internal standard to calculate conversion as well as yield of various products.

See Table 5.1 for more detail.

Entry 1, Table 5.1

To a 2.5 dram vial equipped with a stir bar were added 3.44 mg *p*-TsOH (0.0200 mmol, 0.200 equiv.), 175.5 mg of *N*-H-indole (1.500 mmol, 15.00 equiv.) and 200 μL of standard solution of **137** (0.100 mmol, 1.00 equiv.) (*standard solution*: 21.5 mg of **137**, and 10 μL of undecane as internal standard in 300 μL of DCM). To this an additional 800 μL of DCM was added. The vial was capped and was stirred for 2 h at room temperature. At this point reaction was analyzed by GC using an internal standard to calculate conversion as well as yield of various products.

Entry 2, Table 5.1

The same procedure as described for entry **1** was used, except DCE was used as solvent.

Entry 3, Table 5.1

The same procedure as described for entry **1** was used, except toluene was used as solvent.

Entry 4, Table 5.1

The same procedure as described for entry **1** was used, except DMA was used as solvent.

Entry 5, Table 5.1

To a 2.5 dram vial equipped with a stir bar were added 1.71 mg *p*-TsOH (0.0100 mmol, 0.100 equiv.), 87.8 mg of *N*-H-indole (0.700 mmol, 7.000 equiv.) and 200 μL of standard solution of **137** (0.100 mmol, 1.00 equiv.) (*standard solution*: 21.5 mg of **137**, and 10 μL of undecane as internal standard in 300 μL of DMA). To this an additional

300 μL of DMA was added. The vial was capped and was stirred for 16 h at room temperature. The crude mixture was purified with flash silica-gel column chromatography.

Entry 6, Table 5.1: To a 2.5 dram vial equipped with a stir bar was added 1.71 mg *p*-TsOH (0.0100 mmol, 0.100 equiv.), 117.1 mg of *N*-H-indole (1.00 mmol, 10.0 equiv.) and 200 μL of standard solution of **137** (0.100 mmol, 1.00 equiv.) (*standard solution*: 21.5 mg of **137**, and 10 μL of undecane as internal standard in 300 μL of DMA). To this an additional 300 μL of DMA was added. The vial was capped and was stirred for 16 h at room temperature. The crude mixture was purified with flash silica-gel column chromatography.

Substrate Scope with **137**

General Procedure for Substrate Scope (Table 5.2)

To a 2.5 dram vial equipped with a stir bar were added 5.13 mg of *p*-TsOH (0.030 mmol, 0.100 equiv.), 351.3 mg of *N*-H-indole (3.00 mmol, 10.0 equiv.) and 42.9 mg of **137** (0.300 mmol, 1.00 equiv.). To this 1.5 mL of DMA was added via syringe. The vial was capped and was stirred for given time at room temperature. The crude mixture was purified with flash silica-gel column chromatography. (*Note: In case of liquid nucleophiles, p-TsOH was added last*)

Synthesis of 127

The same procedure as the general procedure was followed. Yield = 80% (average of two run).

The ^{1}H-NMR spectrum of product was matched with literature.

Synthesis of 138

The same procedure as the general procedure was followed. Yield = 81% (average of two run), R_f = 0.30 w/ 20% EtOAC/Hex, pale green solid, M.P. = 51-53 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.37 (s,1 H), 7.66 (d, *J* = 7.9 Hz, 2 H), 7.35 (dt, *J* = 7.2 Hz, *J* = 0.9 Hz, 2 H), 7.30-7.22 (m, 2 H), 7.13 (ddd, *J* = 7.9 Hz, *J* = 7.0 Hz, *J* = 0.8 Hz, 2 H), 6.91 (d, *J* = 2.3 Hz, 1 H), 6.82 (s, 1 H), 4.75 (q, *J* = 7.1 Hz, 1 H), 3.72 (s, 3 H), 1.88 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 137.5, 136.8, 127.5, 127.1, 126.2, 121.9, 121.5, 121.4, 120.3, 120.0, 119.9, 119.2, 118.6, 111.2, 109.3, 32.7, 28.3, 22.2. IR 3411, 2967, 1455, 1335, 760 cm^{-1}. HRMS $C_{19}H_{19}N_2$ $(M+H)^+$ calcd. 275.1543, obsvd. 275.1554.

Synthesis of 139

The same procedure as the general procedure was followed except 432.0 mg of indole **(**3.00 mmol, 10.0 equiv.) was added. Yield = 85% (average of two run), R_f = 0.35 w/ 20% EtOAC/Hex, colorless solid, M.P. = 52-54 °C, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.81 (s, 1 H), 7.64 (d, *J* = 7.9 Hz, 1 H), 7.45 (d, *J* = 7.9 Hz, 1 H), 7.31 (dd, *J* = 12.4 Hz, *J* = 8.1 Hz, 2 H), 7.19-7.15 (m, 2 H), 7.06-7.00 (m, 3 H), 4.72 (qd, *J* = 7.2 Hz, J = 1.1 Hz, 1 H), 3.67 (s, 3 H), 2.40 (s, 3 H), 1.89 (d, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 136.9, 136.8, 131.2, 127.4, 127.1, 121.9, 121.8, 121.1, 120.3, 119.8, 119.5, 119.1, 118.5, 115.2, 111.1, 108.7, 29.6, 29.3, 21.2, 10.7. IR 3419, 1457, 1233, 765 cm^{-1}. HRMS $C_{20}H_{21}N_2$ $(M+H)^+$ calcd. 289.1699, obsvd. 289.1701.

Synthesis of 140

The same procedure as the general procedure was followed except 616.8 mg of 1-methyl-2-phenyl-1*H*-indole **(**3.00 mmol, 10.0 equiv.) and additional 1 mL of DMA were

added. Yield = 55% (average of two run), R_f = 0.32 w/ 20% EtOAC/Hex, colorless solid, M.P. = 178-180 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.80 (s,1 H), 7.67 (d, *J* = 7.9 Hz, 1 H), 7.49-7.43 (m, 3 H), 7.39 (dd, *J* = 7.7 Hz, *J* = 1.6 Hz, 2 H), 7.34 (t, *J* = 8.6 Hz, 1 H), 7.28 (t, *J* = 7.6 Hz, 1 H), 7.21 (td, *J* = 7.6 Hz, *J* = 1.1 Hz, 1 H), 7.13-7.09 (m, 1 H), 7.05-6.94 (m 3 H), 4.55 (dq, *J* = 7.2 Hz, *J* = 0.8 Hz, 1 H), 3.60 (s, 3 H), 1.86 (d, *J* = 7.2 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 137.7, 137.2, 136.7, 132.4, 130.9, 130.8, 128.4, 128.1, 126.8, 121.8, 121.7, 121.4, 121.3, 120.9, 119.9, 118.9, 118.8, 117.4, 110.9, 109.5, 30.9, 28.6, 21.7. IR 3414, 2969, 1466, 740 cm^{-1}. HRMS $C_{25}H_{23}N_2$ $(M+H)^+$ calcd. 351.1856, obsvd. 351.1843.

Synthesis of 141

The same procedure as the general procedure was followed except 588.1 mg of 5-bromo-1*H*-indole (3.00 mmol, 10.0 equiv.) was used. Yield = 46% (average of two run), R_f = 0.30 w/ 20% EtOAC/Hex, colorless solid, M.P. = 47-50 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.88 (s, 2 H), 7.71-7.70 (m, 1 H), 7.54 (dd, *J* = 7.9 Hz, *J* = 0.7 Hz, 1 H), 7.36 (dt, *J* = 8,1 Hz, *J* = 0.8 Hz, 1 H), 7.26-7.16 (m, 3 H), 7.06 (ddd, *J* = 7.9 Hz, *J* = 7.0 Hz, *J* = 0.9 Hz, 1 H), 6.91 (td, *J* = 2.2 Hz, *J* = 0.8 Hz, 2 H), 4.61 (q, *J* = 7.1 Hz, 1 H), 1.79 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 136.8, 135.3, 128.8, 126.9, 124.7, 122.6, 122.3, 122.0, 121.5, 119.8, 119.2, 112.6, 112.5, 111.3, 28.2, 21.7. IR 3405, 1453, 1092, 739 cm^{-1}. HRMS $C_{18}H_{15}BrN_2$ $(M)^+$ calcd. 338.0429, obsvd. 338.0419.

Synthesis of 142

The same procedure as the general procedure was followed except 588.1 mg of 5-bromo-1*H*-indole (3.00 mmol, 10.0 equiv.) was used. Yield = 76% (average of two run), R_f = 0.25 w/ 20% EtOAC/Hex, colorless solid, M.P. = 57-59 °C. ^{1}H-NMR (400 MHz,

$CDCl_3$) δ = 7.86 (s,1 H), 7.75 (s, 1 H), 7.63 (d, *J* = 7.9 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 1 H), 7.23-7.18 (m, 2 H), 7.11-7,06 (m, 2 H), 6.89-6.85 (m, 3 H), 4.66 (q, *J* = 7.1 Hz, 1 H), 3.80 (s, 3 H), 1.83 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 153.7, 136.8, 132.0, 127.4, 127.0, 122.2, 121.9, 121.6, 121.5, 121.4, 119.9, 119.1, 111.9, 102.0, 56.0, 28.3, 21.8. IR 3403, 1452, 1206, 1091, 739 cm^{-1}. HRMS $C_{19}H_{18}N_2O$ $(M+H)^+$ calcd. 291.1492, obsvd. 291.1489.

Synthesis of 143

The same procedure as the general procedure was followed except 435.6 mg of 7-ethyl-1*H*-indole **(**3.00 mmol, 10.0 equiv.) was used. Yield = 62% (average of two run), R_f = 0.35 w/ 20% EtOAC/Hex, pale green solid, M.P. = 50-52 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.78-7.76 (m, 2 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.49-7.47 (m, 1 H), 7.34 (d, *J* = 8.1 Hz, 1 H), 7.19 (td, *J* = 7.6 Hz, *J* = 0.9 Hz, 1 H), 7.10-7.04 (m, 3 H), 6.90-6.86 (m, 2 H), 4.69 (q, *J* = 7.1 Hz, 1 H), 2.85 (q, *J* = 7.6 Hz, 2 H), 1.83 (d, *J* = 7.1 Hz, 3 H), 1.38 (t, *J* = 7.6 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 136.8, 135.6, 127.1, 126.8, 126.5, 122.3, 121.9, 121.8, 121.4, 121.0, 120.4, 119.9, 119.4, 119.1, 117.6, 111.2, 28.4, 24.1, 21.9, 13.9. IR 3403, 1455, 1293, 1091, 739 cm^{-1}. HRMS $C_{20}H_{21}N_2$ $(M+H)^+$ calcd. 289.1699, obsvd. 289.1681.

Synthesis of 144

The same procedure as the general procedure was followed except 393.6 mg of 3-methyl-1*H*-indole **(**3.00 mmol, 10.0 equiv.) was used. Yield = 54% (average of two run), R_f = 0.41 w/ 20% EtOAC/Hex, colorless solid, M.P. = 64-66 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.99 (m, 1 H), 7.59-7.56 (m, 2 H), 7.35 (t, *J* = 8.2 Hz, 2 H), 7.21-7.08 (m, 3 H), 6.99 (t, *J* = 7.5 Hz, 1 H), 4.72 (q, *J* = 7.1 Hz, 1 H), 2.45 (s, 3 H), 1.76 (d, *J* = 7.1 Hz, 3

H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 138.7, 136.7, 135.0, 129.8, 126.9, 122.5, 121.4, 120.9, 119.8, 119.7, 119.5, 119.0, 118.2, 111.2, 110.6, 105.9, 28.6, 20.6, 8.7. IR 3412, 1455, 1335, 740 cm^{-1}. HRMS $C_{19}H_{19}N_2$ $(M+H)^+$ calcd. 275.1543, obsvd. 275.1554.

Synthesis of 145

The same procedure as the general procedure was followed except 201.2 mg of 1*H*-pyrrole **(**3.00 mmol, 10.0 equiv.) was added. Yield = 55% (average of two run), R_f = 0.43 w/ 20% EtOAC/Hex, colorless liquid, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.94-7.78 (m, 2 H), 7.48 (d, *J* = 7.9 Hz, 1 H), 7.37 (d, J = 8.2 Hz, 1 H), 7.22 (td, *J* = 7.6 Hz, *J* = 0.9 Hz, 1 H), 7.11-7.07 (m, 1 H), 6.97 (d, *J* = 2.4 Hz, 1 H), 6.59 (q, *J* = 2.1 Hz, 1 H), 6.21 (q, *J* = 2.9 Hz, 1 H), 6.17-6.16 (m, 1 H), 4.45 (q, *J* = 7.1 Hz, 1 H), 1.74 (d, *J* = 7.1 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 136.7, 129.2, 126.7, 122.3, 121.4, 120.2, 119.7, 119.6, 116.3, 111.3, 108.1, 104.3, 30.0, 21.3. IR 3401, 1291, 1091, 743 cm^{-1}. HRMS $C_{14}H_{14}N_2$ $(M+H)^+$ calcd. 211.123, obsvd. 211.1224.

Synthesis of 146

The same procedure as the general procedure was followed except 525.5 mg of methyl indolizine-1-carboxylate **(**3.00 mmol, 10.0 equiv.) was used. Yield = 68% (average of two run), R_f = 0.28 w/ 20% EtOAC/Hex, colorless solid, M.P. = 77-79 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.22 (d, *J* = 9.0 Hz, 1 H), 8.11 (s, 1 H), 7.68 (d, *J* = 7.1 Hz, 1 H), 7.61 (d, *J* = 7.9 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 7.31 (s, 1 H), 7.23-7.19 (m, 1 H), 7.12 (t, *J* = 7.5 Hz, 1 H), 6.98 (dd, *J* = 9.0 Hz, *J* = 6.6 Hz, 1 H), 6.59 (d, *J* = 2.4 Hz, 1 H), 6.52 (td, *J* = 6.8 Hz, *J* =0.7 Hz, 1 H), 4.57 (q, *J* = 7.0 Hz, 1 H), 3.93 (s, 3 H), 1.85 (d, *J* = 7.0 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 165.7, 136.8, 136.3, 129.1, 126.4, 124.0, 122.3, 121.8, 121.5, 119.8, 119.6, 118.8, 117.9, 113.6, 112.1, 111.6, 102.4,

51.0, 28.6, 20.8. IR 3314, 2966, 1662, 1214, 735 cm^{-1}. HRMS $C_{20}H_{19}N_2O_2$ $(M+H)^+$ calcd. 319.1441, obsvd. 319.1453.

Synthesis of 147

The same procedure as the general procedure was followed except reaction was run at 70 °C. Yield = 84% (average of two run), R_f= 0.40 w/ 20% EtOAC/Hex, colorless solid, M.P. = 88-90 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 7.82 (s,1 H), 7.64 (dt, *J* = 7.9 Hz, *J* = 0.9 Hz, 2 H), 7.33-7.29 (m, 2 H), 7.26-7.32 (m, 2 H), 7.07 (ddd, *J* = 8.0 Hz, *J* = 7.0 Hz, *J* = 1.1 Hz, 2 H), 6.99 (d, *J* = 1.6 Hz, 1 H), 6.86 (s, 1 H), 4.41 (t, *J* = 7.4 Hz, 1 H), 3.72 (s, 3 H), 2.27 (quintet, *J* = 7.4 Hz, 2 H) 1.05 (t, *J* = 7.4 Hz, 3 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 137.4, 136.7, 128.2., 127.8, 127.4, 126.5, 121.8, 121.6, 121.4, 120.6, 120.0, 119.1, 119.0, 118.6, 111.2, 109.3, 36.0, 32.7, 29.1, 13.3. IR 3406, 2963, 1584, 1451, 1335, 1095, 738 cm^{-1}. HRMS $C_{20}H_{21}N_2$ $(M+H)^+$ calcd. 289.1699, obsvd. 289.1705.

Substrate Scope with **148**

General Procedure for Substrate Scope (Table 5.3)

To a 2.5 dram vial equipped with a stir bar were added 3.44 mg of *p*-TsOH (0.020 mmol, 0.100 equiv.), 262.4 mg of *N*-Me-indole (2.00 mmol, 10.0 equiv.) and 59.7 mg of **148** (0.200 mmol, 1.00 equiv.). To this 1.0 mL of DMA was added via syringe. The vial was capped and was stirred for given time at 70 °C in oil bath. The crude mixture was purified with flash silica-gel column chromatography. (*Note: In case of liquid nucleophiles, p-TsOH was added last*)

Synthesis of 149

The same procedure as the general procedure was followed. Yield = 91% (average of two run), R_f = 0.35 w/ 66% EtOAC/Hex, colorless solid, M.P. = 133-135 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 1 H), 7.52 (dd, *J* = 12.1 Hz, *J* = 9.1 Hz, 2 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.26 (d, *J* = 8.2 Hz, 1 H), 7.16-7.08 (m, 2 H), 7.03 (d, *J* = 2.5 Hz, 1 H), 6.96-6.90 (m, 3 H), 3.73 (s, 3 H), 3.65-3.55 (m, 4 H), 2.62 (t, *J* = 5.4 Hz, 4 H), 1.52 (s, 9 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.4, 137.9, 137.3, 126.9, 126.5, 126.1, 122.3, 121.8, 121.6, 121.4, 121.2, 120.4, 118.9, 118.4, 111.4, 109.4, 79.4, 38.1, 35.9, 32.9, 28.7. IR 3303, 2947, 1667, 734 cm^{-1}. HRMS $C_{27}H_{31}N_3O_2$ $(M+Na)^+$ calcd. 452.2308, obsvd. 452.2314.

Synthesis of 150

The same procedure as the general procedure was followed. Yield = 90% (average of two run), R_f = 0.35 w/ 66% EtOAC/Hex, colorless solid, M.P. = 186-188 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.10 (d, *J* = 1.1 Hz, 1 H), 8.01 (d, *J* = 1.2 Hz, 1 H), 7.49 (d, *J* = 8.0 Hz, 1 H), 7.29 (d, *J* = 8.1 Hz, 1 H), 7.18 (d, *J* = 8.8 Hz, 1 H), 7.10-7.02 (m, 3 H), 6.90 (dd, *J* = 3.8 Hz, *J* = 1.7 Hz, 1 H), 6.75 (dd, *J* = 8.8 Hz, *J* = 2.4 Hz, 1 H), 3.66 (s, 3 H), 3.58 (bs, 4 H), 2.63-2.52 (m, 4 H), 1.49 (s, 9 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.4, 153.1, 137.3, 132.5, 129.2, 126.6, 126.1, 123.0, 122.2, 121.7, 121.6, 121.4, 121.2, 118.9, 111.8, 111.4, 11.2, 104.0, 79.5, 55.9, 37.9, 35.7, 20.7. IR 3305, 1524, 1425, 793 cm^{-1}. HRMS $C_{27}H_{31}N_3O_3$ $(M+Na)^+$ calcd. 468.2258, obsvd. 468.2267.

Synthesis of 151

The same procedure as the general procedure was followed. Yield = 71% (average of two run), R_f = 0.30 w/ 66% EtOAC/Hex, colorless solid, M.P. = 266-268 °C,

^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.35 (d, *J* = 0.4 Hz, 1 H), 8.12 (d, *J* = 0.6 Hz, 1 H), 8.05 (d, *J* = 0.9 Hz, 1 H), 7.56 (dd, *J* = 8.6 Hz, *J* = 1.5 Hz, 1 H), 7.45 (d, *J* = 8.6 Hz, 1 H), 7.40 (d, *J* = 8.1 Hz, 1 H), 7.31 (d, *J* = 8.1 Hz, 1 H), 7.25 (d, *J* = 2.5 Hz, 1 H), 7.11-7.05 (m, 2 H), 6.90-6.86 (m, 1 H), 3.87 (s, 3 H), 3.57 (bs, 4 H), 2.64-2.51 (m, 4 H), 1.48 (s, 9 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.3, 137.2, 136.5, 129.7, 125.9, 125.2, 123.4, 122.7, 122.0, 121.9, 121.4, 121.0, 120.6, 119.9, 119.0, 113.7, 111.4, 79.6, 52.0, 37.9, 35.8, 28.6. IR 3303, 1667, 1509, 734 cm^{-1}. HRMS $C_{28}H_{32}N_3O_4$ $(M+H)^+$ calcd. 474.2401, obsvd. 474.2401.

Synthesis of 152

The same procedure as the general procedure was followed. Yield = 85% (average of two run), R_f = 0.32 w/ 66% EtOAC/Hex, colorless thick liquid, ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.14 (s, 1 H), 7.70 (d, *J* = 0.6 Hz, 1 H), 7.35 (dt, *J* = 7.3 Hz, *J* = 0.9 Hz, 1 H), 7.15 (td, *J* = 7.6 Hz, *J* = 1.1 Hz, 1 H), 7.01-6.96 (m, 2 H), 6.55 (td, *J* = 2.6 Hz, *J* = 1.5 Hz, 1 H), 6.23-6.16 (m, 2 H), 3.60 (ddd, *J* = 13.3 Hz, *J* = 7.5 Hz, *J* = 3.9 Hz, 2 H), 3.49-3.44 (m, 2 H), 2.47-2.41 (m, 2 H), 2.26 (ddd, *J* = 13.3 Hz, 8.5 Hz, *J* = 4.3 Hz, 2 H), 1.47 (s, 9 H). ^{13}C-NMR {^{1}H} (100 MHz, $CDCl_3$) δ = 155.2, 137.7, 137.1, 125.8, 122.3, 122.1, 120.9, 120.8, 119.7, 116.6, 111.4, 108.0, 104.9, 79.5, 38.3, 36.6, 28.6. IR 3369, 2969, 2928, 1594, 1484, 1381, 789 cm^{-1}. HRMS $C_{22}H_{28}N_3O_2$ $(M+H)^+$ calcd. 366.2176, obsvd. 366.2182.

Synthesis of 153

The same procedure as the general procedure was followed. Yield = 90% (average of two run), R_f = 0.30 w/ 66% EtOAC/Hex, colorless solid, M.P. = 197-199 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 8.62 (d, *J* = 1.7 Hz, 1 H), 8.17 (dt, *J* = 9.0 Hz, *J* = 1.1

Hz, 1 H), 7.84 (d, *J* = 7.2 Hz, 1 H), 7.54 (s, 1 H), 7.30 (d, *J* = 8.2 Hz, 1 H), 7.21 (d, *J* = 2.5 Hz, 1 H), 7.05 (ddd, *J* = 8.1 Hz, *J* = 7.1 Hz, *J* = 1.0 Hz, 1 H), 6.98 (d, *J* = 8.1 Hz, 1 H), 6.85 (ddd, *J* = 9.0 Hz, 6.6 Hz, *J* = 0.9 Hz, 1 H), 6.78 (ddd, *J* = 8.1 Hz, 7.1 Hz, *J* = 0.9 Hz, 1 H), 6.31 (td, *J* = 6.9 Hz, *J* = 1.3 Hz, 1 H), 3.95 (s, 3 H), 3.73 (bs, 2 H), 3.48 (bs, 2 H), 2.5 (m, 4 H), 1.48 (s, 9 H). ^{13}C-NMR $\{^{1}H\}$ (100 MHz, $CDCl_3$) δ = 165.8, 155.1, 137.1, 136.9, 129.2, 128.8, 125.4, 125.1, 122.3, 121.7, 121.6, 120.0, 119.9, 119.6, 119.3, 115.7, 111.7, 111.4, 102.5, 79.8, 51.1, 37.9, 28.6. IR 3303, 1667, 1509, 734 cm^{-1}. HRMS $C_{28}H_{32}N_3O_4$ $(M+H)^+$ calcd. 474.2387, obsvd. 474.2397.

Biological Evaluation

General Culture Procedure

MCF-10A and MCF-7 cells were cultured in monolayer in Dulbecco's Modified Eagle's Medium/Nutrient Mixture F-12 Ham (DME/F-12) containing HEPES buffer and L-glutamine (HyClone) supplemented with 10% (v/v) fetal bovine serum (FBS, HyClone), 1% (v/v) penicillin/streptomycin (P/S), 1% (v/v) insulin-transferrin-selenium-X (ITS, Gibco), and 2.5 nM human epidermal growth factor, recombinant (EFG, BD Biosciences). Cells were maintained in a humidified incubator at 37 °C and 5% CO_2.

Initial 3-point Screening of Compounds 138-147, 149-153

In a 96-well flat bottom plate, MCF-7 cells were seeded at 1,500 cells/well and MCF-10A cells were seeded at 9,000 cells/well using the 10% FBS medium described in the general culture procedure. The cells were then incubated in a humidified incubator at 37 °C and 5% CO_2 for 18 hours. From a 100 mM stock of each compound in molecular biology grade DMSO (Sigma) was made a 50 μM standard solution of each compound in DME/F-12 supplemented with 2% (v/v) FBS, 1% (v/v) P/S, 1% (v/v) ITS, and 2.5 nM

EFG. From this 50 μM standard solution, serial dilutions of 10 μM and 1 μM were made. The media was aspirated from the cells in the 96-well plates after the initial incubation period and 100 μL of the appropriately diluted compound in media was added (day 0). The cells were incubated and on days 2, and 4, the media was aspirated and 100 μL of fresh compound-containing media was added. On day 5, an MTS assay was performed using CellTiter 96 AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). The absorbance measurements were normalized to the DMSO control and these values were plotted against the ± standard deviation of 2 wells per condition.

12-Point Dose Response Curve of Compounds 139 and 149

In a 96-well flat bottom plate, MCF-7 cells were seeded at 1,500 cells/well and MCF-10A cells were seeded at 9,000 cells/well using the 10% FBS medium described in the general culture procedure. The cells were then incubated in a humidified incubator at 37 °C and 5% CO_2 for 18 hours. From a 100 mM stock of each compound in molecular biology grade DMSO (Sigma) was made a 100 μM standard solution of each compound in DME/F-12 supplemented with 2% (v/v) FBS, 1% (v/v) P/S, 1% (v/v) ITS, and 2.5 nM EFG. From this 100 μM standard solution, an automated liquid handler (EP Motion 5075, Eppendorf) was used to prepare the 12 necessary concentrations. The media was aspirated from the cells in the 96-well plates after the initial incubation period and 100 μL of the appropriate compound in media was added (day 0). The cells were incubated and on days 2 and 4, the media was aspirated and 100 μL of fresh compound-containing media was added. On day 5, an MTS assay was performed using CellTiter 96 AQ_{ueous} Non-Radioactive Cell Proliferation Assay (Promega). The absorbance measurements were normalized to the DMSO control and these values were plotted against the ±

standard deviation of the 3 wells per condition. The EC_{50} values were calculated using GraphPad Prism (v5.0) software, nonlinear fit, log(inhibitor) vs. response – variable slope (four parameters).

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